Clinical trial results:
A Multicenter, Single-arm, Open-label Study with Pomalidomide in Combination with Low Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma.

Summary

EudraCT number	2012-001888-78
Trial protocol	ES PT SE NL DE FI AT GR GB DK IT BE IE NO SK SI EE PL FR
Global end of trial date	11 December 2019

Results information

Result version number	v1 (current)
This version publication date	11 December 2020
First version publication date	11 December 2020

Trial information

Trial identification

Sponsor protocol code	CC-4047-MM-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01712789
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	11 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety of the combination of pomalidomide (POM) and low dose dexamethasone (LD-DEX) in a large cohort of subjects with refractory multiple myeloma (MM) or relapsed and refractory MM.

Protection of trial subjects:

Informed Consent, Patient Confidentiality, Archival of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 54
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Greece: 54
Country: Number of subjects enrolled	Ireland: 18
Country: Number of subjects enrolled	Italy: 219
Country: Number of subjects enrolled	Netherlands: 23
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 85
Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United Kingdom: 51

Worldwide total number of subjects	682
EEA total number of subjects	664

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)	290
From 65 to 84 years	387
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 112 sites: 4 in Austria, 7 in Belgium, 3 in Denmark, 1 in Estonia, 2 in Finland, 13 in France, 17 in Germany, 1 in Greece, 3 in Ireland, 15 in Italy, 5 in the Netherlands, 2 in Norway, 3 in Poland, 4 in Portugal, 1 in Slovakia, 15 in Spain, 2 in Sweden, 3 in Switzerland, 2 in Turkey, and 9 in the United Kingdom.

Pre-assignment

Screening details:

Study participants had to have either refractory or relapsed and refractory disease, defined as documented disease progression during or within 60 days of completing their last myeloma therapy to be eligible to participate in the trial.

Period 1

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

Arms

Arm title	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)

Arm description:

Participants received 4 mg pomalidomide (POM) by mouth (PO) on Days 1 to 21 of each 28-day treatment cycle and low dose dexamethasone (LD-Dex) PO at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle until the documentation of confirmed progressive disease (PD), intolerable toxicity, death, withdrawal of participation in the study/consent, lost to follow-up, or as long as they benefited from therapy according to the opinion of the responsible study investigator.

Arm type	Experimental
Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	CC-4047
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules for oral administration

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	DEX
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets for oral administration

Number of subjects in period 1	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)
Started	682
Received Study Treatment	676
Completed	0
Not completed	682
Adverse event, serious fatal	57
Consent withdrawn by subject	21
Adverse event, non-fatal	52
Transition to Commercial Treatment	8
Miscellaneous	31
Lost to follow-up	1
Progressive disease	504
Participants did not receive study drug	6
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)
Reporting group description:	
Participants received 4 mg pomalidomide (POM) by mouth (PO) on Days 1 to 21 of each 28-day treatment cycle and low dose dexamethasone (LD-Dex) PO at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle until the documentation of confirmed progressive disease (PD), intolerable toxicity, death, withdrawal of participation in the study/consent, lost to follow-up, or as long as they benefited from therapy according to the opinion of the responsible study investigator.	

Reporting group values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)	Total	
Number of subjects	682	682	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	290	290	
From 65-84 years	387	387	
85 years and over	5	5	
Age Continuous Units: Years			
arithmetic mean	65.4		
standard deviation	± 9.10	-	
Sex: Female, Male Units: Participants			
Female	301	301	
Male	381	381	
Race/Ethnicity, Customized Units: Subjects			
Asian	3	3	
Black or African American	4	4	
White	669	669	
Other	2	2	
Missing	4	4	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	52	52	
Not Hispanic or Latino	626	626	
Unknown or Not Reported	4	4	
Eastern Cooperative Oncology Group (ECOG) Performance Status			

ECOG performance status is used to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: -0 = Fully active, no restrictions; 1 = Restricted activity but ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities; 3 = Limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled, no self-care, confined to bed or chair; 5 = Dead			
Units: Subjects			
0 = Fully active, no restrictions	295	295	
1 = Restricted activity but ambulatory	319	319	
2 = Ambulatory and capable of all self-care	67	67	
3 = Limited self-care	1	1	
4 = Completely disabled	0	0	
Serum Light Chain Type			
Light chains are proteins made by plasma cells and make immunoglobulins (antibodies). Immunoglobulins help protect the body against illness and infections. Immunoglobulins are formed when light chains link up with heavy chains, another type of protein. There are two types of light chains: lambda and kappa light chains. A free light chains test measures the amount of lambda and kappa free light chains in the blood. If the amount of free light chains is higher or lower than normal, it can mean you have a disorder of the plasma cells.			
Units: Subjects			
Kappa	364	364	
Lambda	230	230	
No Serum Light chain Type Detected	16	16	
Test Not Performed	72	72	
Serum Heavy Chain Type			
Immunoglobulins help protect the body against illness and infections. Immunoglobulins are formed when light chains link up with heavy chains, another type of protein.			
Units: Subjects			
Immunoglobulin A (IgA)	145	145	
Immunoglobulin D (IgD)	5	5	
Immunoglobulin E (IgE)	0	0	
Immunoglobulin G (IgG)	388	388	
Immunoglobulin M (IgM)	4	4	
No serum heavy chain type detected	68	68	
Test not performed	72	72	
Renal Function (Cockcroft Gault Creatinine Clearance) Units: Subjects			
< 30 mL/min	12	12	
30 - < 45 mL/min	57	57	
45 - < 60 mL/min	168	168	
60 - < 80 mL/min	190	190	
≥ 80 mL/min	250	250	
Missing	5	5	
Time Since Diagnosis Units: Years			
arithmetic mean	6.15		
standard deviation	± 3.649	-	
Beta 2 Microglobulin			
This test measures the amount of a protein called beta-2 microglobulin (B2M) in the blood.			
Units: mg/L			
arithmetic mean	5.48		

standard deviation	± 4.713	-	
Corrected Serum Calcium			
Units: mmol/L			
arithmetic mean	2.43		
standard deviation	± 0.231	-	

End points

End points reporting groups

Reporting group title	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)

Reporting group description:

Participants received 4 mg pomalidomide (POM) by mouth (PO) on Days 1 to 21 of each 28-day treatment cycle and low dose dexamethasone (LD-Dex) PO at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle until the documentation of confirmed progressive disease (PD), intolerable toxicity, death, withdrawal of participation in the study/consent, lost to follow-up, or as long as they benefited from therapy according to the opinion of the responsible study investigator.

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)[1]

End point description:

Adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during course of study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, regardless of etiology. Any worsening (i.e., any significant adverse change in the frequency or intensity of a pre-existing condition) was considered an AE. Severity of AEs were graded based on the symptoms according to version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events. Second primary malignancies were monitored as events of interest and considered as part of the assessment of AEs.
A SAE = AE occurring at any dose that:
• Results in death;
• Is life-threatening
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity
• Is a congenital anomaly/birth defect

Safety pop. analyzed

End point type	Primary

End point timeframe:

From the first dose of study treatment up to 28 days following the last dose of study treatment. The median duration of treatment with pomalidomide and LD-dex was 21.4 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	676			
Units: Participants				
≥ TEAE	673			
≥ 1 TEAE Related to Pomalidomide (POM)	527			
≥ 1 TEAE Related to LD-Dex	448			
≥ 1 TEAE Related to Either POM or LD-Dex	575			
≥ 1 Grade (Gr) 3 or 4 TEAE	606			
≥ 1 Gr 3 or 4 TEAE Related to (R/T) POM	417			

≥ 1 Gr 3 or 4 TEAE R/T LD-Dex	226			
≥ 1 Gr 3 or 4 TEAE R/T Either POM or LD-Dex	448			
≥ 1 Grade 5 TEAE	127			
≥ 1 Grade 5 TEAE R/T POM	14			
≥ 1 Grade 5 TEAE R/T LD-Dex	16			
≥ 1 Grade 5 TEAE R/T either POM or LD-Dex	18			
≥ 1 Serious TEAE	448			
≥ 1 Serious TEAE R/T POM	187			
≥ 1 Serious TEAE R/T LD-Dex	146			
≥ 1 Serious TEAE R/T Either POM or LD-Dex	215			
≥ 1 Serious TEAE Leading to (L/T)Stopping of POM	36			
≥ 1 Serious TEAE L/T Stopping of LD-Dex	34			
≥1 Serious TEAE L/T Stopping either POM or LD-Dex	37			
≥ 1 TEAE L/T to Stopping of POM	54			
≥ 1 TEAE L/T to Stopping of LD-DEX	61			
≥ 1 TEAE L/T to Stopping of Either POM or LD-DEX	63			
≥1 Study Drug Related TEAE (L/T) Stopping POM	30			
≥1 Study Drug Related TEAE L/T Stopping LD-Dex	19			
≥1 Drug Related TEAE L/T Stopping LD-Dex or POM	38			
≥ 1 TEAE L/T to Reduction (R/D) of POM	164			
≥ 1 TEAE L/T to R/D of LD-DEX	150			
≥ 1 TEAE L/T to R/D of Either POM or LD-DEX	244			
≥ 1 Study Drug Related TEAE L/T to R/D of POM	142			
≥ 1 Study Drug Related TEAE L/T to R/D of LD-DEX	135			
≥1 StudyDrug Related TEAE L/T to R/D POM or LD-DEX	224			
≥ 1 TEAE L/T to Interruption (I/R) of POM	455			
≥ 1 TEAE L/T to I/R of LD-DEX	434			
≥ 1 TEAE L/T to I/R of either POM or LD-DEX	470			
≥ 1 Study Drug Related TEAE L/T to I/R of POM	294			
≥ 1 Study Drug Related TEAE L/T to I/R of LD-DEX	185			
≥1 StudyDrug Related TEAE L/T to I/R POM or LD-DEX	333			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

End point title	Overall Response

End point description:

Overall response rate (ORR) was defined as the percentage of participants with a stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) according to the International Myeloma Working Group uniform response criteria (IMWG URC) assessed by the Investigator. Responses must have been confirmed at at least 2 consecutive assessments before the institution of any new therapy with no known evidence of progressive or new bone lesions.

End point type	Secondary

End point timeframe:

Response was assessed at each treatment cycle and at treatment discontinuation; median duration of treatment with pomalidomide and LD-dex was 21.4 weeks

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	682			
Units: Percentage of Participants				
number (confidence interval 95%)	33.4 (29.9 to 37.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from treatment enrollment to the first documentation of response (sCR, CR, VGPR or PR) based on IMWG criteria.

Analysis Population Description: Participants with a response (SCR, CR, VGPR or PR)

End point type	Secondary

End point timeframe:

Response was assessed at each treatment cycle and at treatment discontinuation; median duration of treatment with pomalidomide and LD-dex was 21.4 weeks

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Weeks				
median (full range (min-max))	8.1 (2 to 112)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Duration of Response

End point title	Kaplan Meier Estimate of Duration of Response

End point description:

Duration of response, calculated for responders only, was defined as time from the initial documented response (SCR, CR, VGPR or PR) to the first confirmed disease progression, or death if no disease progression was recorded. Participants without a documented progression were censored at the time of their last tumor assessment.

Analysis Population Description: Participants with a response (SCR, CR, VGPR or PR)

End point type	Secondary

End point timeframe:

From enrollment to the end of follow-up; median time on follow-up was 10.9 (range 0 - 81) months

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	228			
Units: Months				
median (confidence interval 95%)	7.9 (6.48 to 8.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Progression Free Survival (PFS) According to the European Medicines Agency Guidelines

End point title	Kaplan Meier Estimate of Progression Free Survival (PFS) According to the European Medicines Agency Guidelines

End point description:

Progression free survival was calculated as the time from study enrollment, defined as the IVRS enrollment date, until either PD or death (any cause). Participants without an event (either a documented PD or death) at the time of study end were censored at the time of their last documented disease assessment or at the IVRS enrollment date if no disease assessment was conducted.

End point type	Secondary

End point timeframe:

From enrollment to the end of follow-up; median time on follow-up was 10.9 (range 0 - 81) months

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	682			
Units: Months				
median (confidence interval 95%)	4.6 (3.91 to 4.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Time to Progression

End point title	Kaplan Meier Estimate of Time to Progression

End point description:

Time to progression was calculated as the time from study enrollment until first recorded disease progression as determined by the site investigator based on the IMWG criteria, or until death due to progression. Participants not experiencing a documented progression were censored at the time of their last tumor assessment (or at the time of trial enrollment if no assessment was conducted).

End point type	Secondary

End point timeframe:

From enrollment to the end of follow-up; median time on follow-up was 10.9 (range 0 - 81) months

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	682			
Units: Months				
median (confidence interval 95%)	4.8 (4.27 to 5.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Overall Survival (OS)

End point title	Kaplan Meier Estimate of Overall Survival (OS)

End point description:

Overall survival was calculated as the time from study enrollment, defined as the IVRS enrollment date,

until death due to any cause. Participants who did not have death data at the time of study end/analysis were censored at the time they were last known to be alive.

End point type	Secondary

End point timeframe:

From enrollment to the end of follow-up; median time on follow-up was 10.9 (range 0 - 81) months

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	682			
Units: Months				
median (confidence interval 95%)	11.9 (10.65 to 13.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pomalidomide Exposure - Apparent (Oral) Clearance (CL/F)

End point title	Pomalidomide Exposure - Apparent (Oral) Clearance (CL/F)

End point description:

Pharmacokinetic (PK) parameters are derived from pomalidomide concentration versus time data.

Pomalidomide population pharmacokinetics (PopPK) and exposure response (ER) relationships in participants with relapsed and/or refractory MM have been well characterized in two phase 3 trials, i.e., CC-4047-MM-003 and CC-4047-MM-007, separately. Given the similar patient population enrolled in the current CC-4047-MM-010 study, the sponsor believes that additional PopPK and ER analyses would be redundant and would not provide accrued information/value. As such, the sponsor made the decision to not perform these analyses again in the CC-4047-MM-010 study

End point type	Secondary

End point timeframe:

Cycles 1, 2, 3, 4, 5, 6

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Liters/hour				
geometric mean (geometric coefficient of variation)	()			

Notes:

[2] - See endpoint description for 0 participants analyzed reasoning

Statistical analyses

No statistical analyses for this end point

Secondary: Cytogenetic Analysis

End point title	Cytogenetic Analysis

End point description:

Cytogenetic analysis was to be performed using fluorescence in situ hybridization (FISH) methodology at a local laboratory, to evaluate the relationship between cytogenetic profiles and the combination of POM and LD-DEX in terms of response and outcome.

Due to variabilities in site analysis and also data collection methods these data were not analyzed as the quality of the data could not be guaranteed, and the results would hence be unreliable.

End point type	Secondary

End point timeframe:

Study entry

End point values	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: units NA				
number (not applicable)				

Notes:

[3] - See endpoint description for 0 participants analyzed reasoning.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality reported from enrollment to end of follow-up; median time on follow-up was 10.9 (range 0 - 81) months.
Adverse events reported from first dose of study drug up to 28 days after last dose; median duration of treatment was 21.4 weeks.

Adverse event reporting additional description:

Second primary malignancies were monitored as events of interest and considered as part of the assessment of AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)

Reporting group description:

Participants received 4 mg pomalidomide (POM) by mouth (PO) on Days 1 to 21 of each 28-day treatment cycle and low dose dexamethasone (LD-Dex) PO at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle until the documentation of confirmed progressive disease (PD), intolerable toxicity, death, withdrawal of participation in the study/consent, lost to follow-up, or as long as they benefited from therapy according to the opinion of the responsible study investigator.

Serious adverse events	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)		
Total subjects affected by serious adverse events			
subjects affected / exposed	448 / 676 (66.27%)		
number of deaths (all causes)	598		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	6 / 676 (0.89%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stromal tumour			

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Invasive breast carcinoma				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to meninges				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoclonal gammopathy				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Plasma cell leukaemia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Plasma cell myeloma				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 2			
Plasmacytoma				
subjects affected / exposed	10 / 676 (1.48%)			
occurrences causally related to treatment / all	0 / 24			
deaths causally related to treatment / all	0 / 2			
Squamous cell carcinoma				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	7 / 676 (1.04%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the tongue				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic stenosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	6 / 676 (0.89%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				

subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 676 (0.74%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	4 / 676 (0.59%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Disease progression			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Euthanasia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	5 / 676 (0.74%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	45 / 676 (6.66%)		
occurrences causally related to treatment / all	1 / 57		
deaths causally related to treatment / all	0 / 35		
Generalised oedema			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperpyrexia			

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain				

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	41 / 676 (6.07%)			
occurrences causally related to treatment / all	16 / 51			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Social stay hospitalisation				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Scrotal cyst				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	15 / 676 (2.22%)			
occurrences causally related to treatment / all	5 / 17			
deaths causally related to treatment / all	0 / 1			
Dyspnoea exertional				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Orthopnoea				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	6 / 676 (0.89%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 1			
Pleurisy				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Productive cough				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	1 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Respiratory acidosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	14 / 676 (2.07%)			
occurrences causally related to treatment / all	6 / 18			
deaths causally related to treatment / all	1 / 3			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disorientation				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatinine increased				
subjects affected / exposed	6 / 676 (0.89%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Blood immunoglobulin A increased				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoclonal immunoglobulin present				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Protein urine present				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
White blood cell count decreased				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Febrile nonhaemolytic transfusion reaction				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Femur fracture				

subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Ilium fracture				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perineal injury				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post-traumatic pain				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				

subjects affected / exposed	17 / 676 (2.51%)		
occurrences causally related to treatment / all	5 / 19		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac amyloidosis			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 2		
Cardiac disorder			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	12 / 676 (1.78%)		
occurrences causally related to treatment / all	4 / 18		
deaths causally related to treatment / all	0 / 4		
Cardiac failure congestive			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Coronary artery stenosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 3			
Nodal arrhythmia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cauda equina syndrome				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cognitive disorder				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Disturbance in attention				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Facial nerve disorder				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Headache				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IIIrd nerve paresis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial aneurysm				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lateral medullary syndrome				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Motor dysfunction				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parkinsonism				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensorimotor neuropathy				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ruptured cerebral aneurysm				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 676 (2.22%)		
occurrences causally related to treatment / all	8 / 19		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	34 / 676 (5.03%)		
occurrences causally related to treatment / all	30 / 37		
deaths causally related to treatment / all	0 / 0		
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperviscosity syndrome			
subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Leukopenia			

subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	20 / 676 (2.96%)		
occurrences causally related to treatment / all	19 / 22		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	13 / 676 (1.92%)		
occurrences causally related to treatment / all	10 / 14		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exophthalmos			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal fistula			

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	6 / 676 (0.89%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal amyloidosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal infarction				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Rectal haemorrhage				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal ulcer				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder obstruction				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver disorder				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin necrosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	26 / 676 (3.85%)			
occurrences causally related to treatment / all	1 / 33			
deaths causally related to treatment / all	0 / 3			
Crush syndrome				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oliguria				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	23 / 676 (3.40%)			
occurrences causally related to treatment / all	2 / 26			
deaths causally related to treatment / all	0 / 2			
Renal impairment				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal vascular thrombosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	7 / 676 (1.04%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 1			
Bone lesion				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	7 / 676 (1.04%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Gouty arthritis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Osteolysis				

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	7 / 676 (1.04%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacterial diarrhoea				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary sepsis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	9 / 676 (1.33%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	1 / 1			
Bursitis infective				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebral aspergillosis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Citrobacter infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridial sepsis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				

subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	4 / 676 (0.59%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	2 / 2			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Folliculitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster infection neurological				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	14 / 676 (2.07%)			
occurrences causally related to treatment / all	6 / 20			
deaths causally related to treatment / all	0 / 1			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Leishmaniasis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Listeria sepsis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Listeriosis				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	22 / 676 (3.25%)			
occurrences causally related to treatment / all	15 / 31			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	16 / 676 (2.37%)			
occurrences causally related to treatment / all	5 / 19			
deaths causally related to treatment / all	1 / 4			
Meningitis pneumococcal				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Meningococcal sepsis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neutropenic sepsis				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 1			
Oral fungal infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oral infection				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis bacterial				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis externa				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumococcal sepsis				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	117 / 676 (17.31%)			
occurrences causally related to treatment / all	82 / 143			
deaths causally related to treatment / all	6 / 14			
Pneumonia influenzal				

subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	1 / 1			
Pneumonia pneumococcal				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory moniliasis				

subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	11 / 676 (1.63%)			
occurrences causally related to treatment / all	5 / 16			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	14 / 676 (2.07%)			
occurrences causally related to treatment / all	2 / 18			
deaths causally related to treatment / all	0 / 8			
Septic shock				
subjects affected / exposed	15 / 676 (2.22%)			
occurrences causally related to treatment / all	6 / 19			
deaths causally related to treatment / all	1 / 10			
Sinusitis bacterial				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				

subjects affected / exposed	3 / 676 (0.44%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	1 / 1			
Staphylococcal skin infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Systemic candida				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Systemic infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Tracheobronchitis				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	8 / 676 (1.18%)			
occurrences causally related to treatment / all	4 / 9			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	11 / 676 (1.63%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 676 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	5 / 676 (0.74%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperamylasaemia				
subjects affected / exposed	1 / 676 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				

subjects affected / exposed	30 / 676 (4.44%)		
occurrences causally related to treatment / all	0 / 37		
deaths causally related to treatment / all	0 / 3		
Hyperglycaemia			
subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 676 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 676 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			

subjects affected / exposed	3 / 676 (0.44%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pomalidomide Plus Low Dose Dexamethasone (LD-Dex)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	646 / 676 (95.56%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	49 / 676 (7.25%)		
occurrences (all)	67		
C-reactive protein increased			
subjects affected / exposed	34 / 676 (5.03%)		
occurrences (all)	60		
Neutrophil count decreased			
subjects affected / exposed	47 / 676 (6.95%)		
occurrences (all)	173		
Weight decreased			
subjects affected / exposed	47 / 676 (6.95%)		
occurrences (all)	55		
Nervous system disorders			
Dizziness			
subjects affected / exposed	55 / 676 (8.14%)		
occurrences (all)	79		
Headache			
subjects affected / exposed	49 / 676 (7.25%)		
occurrences (all)	56		
Peripheral sensory neuropathy			
subjects affected / exposed	79 / 676 (11.69%)		
occurrences (all)	128		
Tremor			

subjects affected / exposed	45 / 676 (6.66%)		
occurrences (all)	62		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	327 / 676 (48.37%)		
occurrences (all)	859		
Leukopenia			
subjects affected / exposed	92 / 676 (13.61%)		
occurrences (all)	329		
Neutropenia			
subjects affected / exposed	382 / 676 (56.51%)		
occurrences (all)	1400		
Thrombocytopenia			
subjects affected / exposed	236 / 676 (34.91%)		
occurrences (all)	720		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	155 / 676 (22.93%)		
occurrences (all)	267		
Fatigue			
subjects affected / exposed	197 / 676 (29.14%)		
occurrences (all)	332		
Oedema peripheral			
subjects affected / exposed	108 / 676 (15.98%)		
occurrences (all)	171		
Pyrexia			
subjects affected / exposed	178 / 676 (26.33%)		
occurrences (all)	308		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	34 / 676 (5.03%)		
occurrences (all)	38		
Constipation			
subjects affected / exposed	163 / 676 (24.11%)		
occurrences (all)	204		
Diarrhoea			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	118 / 676 (17.46%) 162 96 / 676 (14.20%) 123 49 / 676 (7.25%) 61		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 141 / 676 (20.86%) 197 117 / 676 (17.31%) 184 47 / 676 (6.95%) 61		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 37 / 676 (5.47%) 44 36 / 676 (5.33%) 40 54 / 676 (7.99%) 60		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 37 / 676 (5.47%) 47 76 / 676 (11.24%) 98		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	42 / 676 (6.21%)		
occurrences (all)	54		
Back pain			
subjects affected / exposed	105 / 676 (15.53%)		
occurrences (all)	146		
Bone pain			
subjects affected / exposed	65 / 676 (9.62%)		
occurrences (all)	86		
Muscle spasms			
subjects affected / exposed	96 / 676 (14.20%)		
occurrences (all)	139		
Muscular weakness			
subjects affected / exposed	35 / 676 (5.18%)		
occurrences (all)	43		
Musculoskeletal chest pain			
subjects affected / exposed	54 / 676 (7.99%)		
occurrences (all)	62		
Musculoskeletal pain			
subjects affected / exposed	37 / 676 (5.47%)		
occurrences (all)	43		
Pain in extremity			
subjects affected / exposed	54 / 676 (7.99%)		
occurrences (all)	72		
Infections and infestations			
Bronchitis			
subjects affected / exposed	70 / 676 (10.36%)		
occurrences (all)	109		
Nasopharyngitis			
subjects affected / exposed	57 / 676 (8.43%)		
occurrences (all)	73		
Pneumonia			
subjects affected / exposed	38 / 676 (5.62%)		
occurrences (all)	50		
Respiratory tract infection			

subjects affected / exposed	58 / 676 (8.58%)		
occurrences (all)	79		
Upper respiratory tract infection			
subjects affected / exposed	50 / 676 (7.40%)		
occurrences (all)	93		
Urinary tract infection			
subjects affected / exposed	54 / 676 (7.99%)		
occurrences (all)	74		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	69 / 676 (10.21%)		
occurrences (all)	84		
Hypercalcaemia			
subjects affected / exposed	40 / 676 (5.92%)		
occurrences (all)	64		
Hyperglycaemia			
subjects affected / exposed	40 / 676 (5.92%)		
occurrences (all)	81		
Hypokalaemia			
subjects affected / exposed	52 / 676 (7.69%)		
occurrences (all)	76		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2013	An additional two hundred and twenty subjects were to be enrolled, bringing the total sample size to approximately 720 subjects. The study was planned to remain open for enrollment for an estimated 18 to 24 months, or until the target number of subjects was reached, whichever occurred first. This increase in the study population was made principally for two reasons: - The sample size increase allowed a more detailed evaluation of the safety profile of Pom + LD-dex and enabled a better characterization of uncommon AEs. - This amendment resulted in a broader collection of cytogenetic data. The increase in sample size lead to an increase of the collected profiles. • To further investigate the role of pomalidomide in different subgroups based on their cytogenetic profile, and also to understand the cytogenetic changes that occur throughout the disease course, cytogenetic profiles were now to be analyzed at study entry and at relapse. • For the exclusion criterion related to neutrophil count at study entry, the limit was lowered to 800/µL. A common symptom of the advanced stages of MM disease of the subject population being enrolled in the trial is low neutrophil count. After discussions with key experts in the field of MM management, it was felt that the lower limit could be adapted while use of GCSF could be recommended when applicable.
30 May 2013	• To clearly define the meaning of the word abstinence that is used in the study inclusion criteria and that is relevant for all female subjects of child-bearing potential who participate in the study. This reflects the preferred wording proposed by the Medicines and Healthcare products Regulatory Agency in the United Kingdom, and this clarification is currently being implemented in all Celgene protocols in the pomalidomide development program. • To clearly define the enrollment of a subject into the study. This had important implications for the time period permitted for the subject to begin taking the first dose of study treatment. • To clearly define that the follow-up phase of the study began directly after the permanent discontinuation of the study treatment by the subject. Additional clarification regarding the scheduling of the 28-day safety follow-up visit was also added throughout the protocol. • Recommendations concerning the use of myeloid and erythroid growth factors for the study population were added and the relevant ESMO guidelines cited. Subjects who received primary prophylaxis for the prevention of neutropenia according to such guidelines were also recommended to receive this support while they were participating in the study, although this was left to the discretion of the investigator. • Clarifications regarding the scheduling of permitted platelet transfusions during the screening phase of the study were added to indicate that the screening platelet assessment was to be performed a minimum of 3 days (72 hours) after the completion of the transfusion. • The definition of PD was made consistent throughout the protocol. Progressive disease in this study must be made according to the IMWG uniform response criteria. • Update of Table 1 (Table of Events), its associated footnotes and Section 6 Procedures to clearly indicate when the cytogenetic testing was required during the course of the study and the details of the samples to be taken.

30 May 2013	• Update of Table 1 (Table of Events) its associated footnotes and Section 6 Procedures to amend the laboratory parameters that were required to be reported at screening and during the subject's participation in the study. Previous studies have shown that some parameters are not relevant to achieve the overall objectives of the study.• The methodology required to locally assess the levels of urine M-protein was expanded to include methods other than urine protein electrophoresis. This was as a result of feedback from participating sites that they had other comparable methods (e.g. nephelometric assessment) that were reliable and validated which could be used in such a population. Clarification that 24-hour urine collection samples obtained as standard of care prior to informed consent could be utilized for screening if collected within 7 days prior to the screening visit. • In order to complete the required skeletal survey of study subjects, sites could now use a CT scan as well as X-ray methods. • To clarify in the pomalidomide dosing modification instructions the minimum levels of neutrophil and platelet counts required to begin a new cycle of study treatment with pomalidomide. The reason for this change was so that there was consistency with the study entry criteria. • There were several updates made to the summaries of the other clinical studies involving pomalidomide that were written in the introductory section of the protocol. This represented the most recent information on pomalidomide that the participating sites were to be made aware of, and included updated citations concerning pomalidomide that had been published since the original version of the protocol was released and a notification that pomalidomide has received marketing authorization in the US in February 2013.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported