Clinical trial results:
A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone Versus Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma

Summary

EudraCT number	2012-000128-16
Trial protocol	BE GB HU DE IT ES SK GR CZ AT BG PL
Global end of trial date	05 February 2018

Results information

Result version number	v1 (current)
This version publication date	13 February 2019
First version publication date	13 February 2019

Trial information

Trial identification

Sponsor protocol code	2011-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01568866
WHO universal trial number (UTN)	-
Other trial identifiers	20130398: Amgen Study ID

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 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare progression-free survival in patients with multiple myeloma who relapsed after 1 to 3 prior therapies treated with carfilzomib plus dexamethasone or bortezomib plus dexamethasone.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in a manner consistent with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. The protocol, protocol amendments, protocol clarification letters, informed consent forms (ICFs), subject dosing diaries, advertisements, and health-related quality of life (HRQL) questionnaires were submitted to 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	72 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 81
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	New Zealand: 23
Country: Number of subjects enrolled	Singapore: 20
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Russian Federation: 44

Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Greece: 38
Country: Number of subjects enrolled	Italy: 80
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	United Kingdom: 29
Worldwide total number of subjects	929
EEA total number of subjects	506

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)	433
From 65 to 84 years	487
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Adults with relapsed multiple myeloma were enrolled between 20 June 2012 and 30 June 2014 at 198 centers in 27 countries in Europe, North America, South America, and the Asia-Pacific region.

Pre-assignment

Screening details:

Randomization was stratified by previous proteasome inhibitor therapy (yes vs no), previous lines of treatment (1 vs 2 or 3), International Staging System stage (I vs II–III), and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group.

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	Bortezomib + DEX

Arm description:

Participants received bortezomib 1.3 mg/m² administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

Arm type	Active comparator
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous bolus use

Dosage and administration details:

Bortezomib is administered as a 3-5 second bolus IV injection or SC injection (in accordance with regulatory approval)

Arm title	Carfilzomib + DEX

Arm description:

Participants received 20 mg/m² carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	PR171
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib is administered over 30 minutes as an infusion.

Number of subjects in period 1	Bortezomib + DEX	Carfilzomib + DEX
Started	465	464
Received Treatment	456	463
Completed	0	0
Not completed	465	464
Adverse event, serious fatal	11	19
Physician decision	40	32
Consent withdrawn by subject	19	13
Adverse event, non-fatal	96	101
Unknown	1	-
Study terminated by sponsor	15	29
Randomized but Not Dosed	9	1
Patient Request	57	72
Protocol Non-compliance	2	4
Lost to follow-up	1	-
Disease Progression	214	193

Baseline characteristics

Reporting groups	
Reporting group title	Bortezomib + DEX
Reporting group description:	
Participants received bortezomib 1.3 mg/m² administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.	
Reporting group title	Carfilzomib + DEX
Reporting group description:	
Participants received 20 mg/m² carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.	

Reporting group values	Bortezomib + DEX	Carfilzomib + DEX	Total
Number of subjects	465	464	929
Age, Customized Units: Subjects			
< 65 years	210	223	433
65 -74 years	189	164	353
≥ 75 years	66	77	143
Age Continuous Units: years			
median	65.0	65.0	
full range (min-max)	30.0 to 88.0	35.0 to 89.0	-
Sex: Female, Male Units: Subjects			
Female	236	224	460
Male	229	240	469
Race/Ethnicity, Customized Units: Subjects			
White	353	348	701
Black	9	8	17
Asian	57	56	113
Native Hawaiian/Other Pacific Islander	0	2	2
Not Reported	45	50	95
Multiple	1	0	1
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	232	221	453
1 (Restrictive but ambulatory)	203	211	414
2 (Ambulatory but unable to work)	30	32	62
Stratification Factor: Prior Proteasome Inhibitor Treatment			

Units: Subjects			
Carfilzomib or bortezomib	253	252	505
No prior carfilzomib or bortezomib	212	212	424
Stratification Factor: Lines of Prior Treatment Units: Subjects			
1 line	229	231	460
2 or 3 lines	236	233	469
Stratification Factor: International Staging System (ISS) Stage			
The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group: - Stage I: β2-microglobulin (β2M) < 3.5 mg/L, albumin >= 3.5 g/dL - Stage II: β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin - Stage III: β2M ≥ 5.5 mg/L			
Units: Subjects			
Stage I	204	205	409
Stage II or III	261	259	520
Stratification Factor: Route of Bortezomib Administration			
The route of bortezomib administration (IV versus SC) was made in accordance with local regulatory approved route of administration. The value for this variable was selected for all participants prior to randomization to treatment group in order to balance the baseline characteristics that led to the choice of the particular route of bortezomib administration between the 2 arms.			
Units: Subjects			
Intravenous	108	108	216
Subcutaneous	357	356	713

End points

End points reporting groups

Reporting group title	Bortezomib + DEX

Reporting group description:

Participants received bortezomib 1.3 mg/m² administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

Reporting group title	Carfilzomib + DEX

Reporting group description:

Participants received 20 mg/m² carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

Primary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was defined as the time from randomization to the earlier of disease progression or death due to any cause. Participants were evaluated for disease response and progression according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) as assessed by an Independent Review Committee (IRC). Median PFS was estimated using the Kaplan-Meier method. Participants with no baseline disease assessments, starting a new anticancer therapy before documentation of disease progression or death, death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or alive without documentation of disease progression before the data cut-off date were censored. "99999" indicates data that could not be estimated.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 10 November 2014; median follow-up time for PFS was 11.1.and 11.9 months in the bortezomib and carfilzomib arms respectively

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	464		
Units: months				
median (confidence interval 95%)	9.4 (8.4 to 10.4)	18.7 (15.6 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival

Statistical analysis description:

The hazard ratio (carfilzomib/bortezomib) was estimated using a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration.

Comparison groups	Bortezomib + DEX v Carfilzomib + DEX

Number of subjects included in analysis	929
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.533
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.437
upper limit	0.651

Notes:

[1] - The PFS interim analysis was to be performed using a group sequential monitoring plan. The monitoring plan included an O'Brien-Fleming type of efficacy stopping boundary constructed using the Lan-DeMets alpha spending function to ensure a 1-sided Type I error rate ≤ 0.025.

[2] - Log rank test stratified by the randomization stratification factors.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) is defined as the time from randomization to the date of death (whatever the cause). Participants who were alive or lost to follow-up as of the data analysis cut-off date were censored at the patient's date of last contact (last known to be alive). Median overall survival was estimated using the Kaplan-Meier method. "99999" indicates data that could not be estimated.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 03 January 2017; median follow-up time for OS was 36.9 and 37.5 months for each treatment group respectively.

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	464		
Units: months				
median (confidence interval 95%)	40.0 (32.6 to 42.3)	47.6 (42.5 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival

Statistical analysis description:

The second interim analysis of overall survival was to be conducted after 394 events had been reached. A one-sided significance level was determined using the O'Brien-Fleming–type α spending function based on the actual number of events (α=0.0123). The hazard ratio (carfilzomib/bortezomib) was estimated using a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration.

Comparison groups	Bortezomib + DEX v Carfilzomib + DEX

Number of subjects included in analysis	929
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.01 [4]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.791
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.648
upper limit	0.964

Notes:

[3] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.
[4] - Log rank test stratified by the randomization stratification factors.

Secondary: Overall Response

End point title	Overall Response

End point description:

Disease response was evaluated according to the IMWG-URC by the IRC. Overall response was defined as the percentage of participants with a best overall response of partial response (PR), very good PR (VGPR), complete response (CR) or stringent CR (sCR).
sCR: As for CR, normal serum free light chain (SFLC) ratio and no clonal cells in bone marrow (BM).
CR: No immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in BM biopsy;
VGPR: Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-protein with urine M-protein <100 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.
PR: ≥ 50% reduction of serum M-protein and reduction in urine M-protein by ≥ 90% or to < 200 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.

End point type	Secondary

End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 10 November 2014; median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group.

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	464		
Units: percentage of participants				
number (confidence interval 95%)	62.6 (58.0 to 67.0)	76.9 (72.8 to 80.7)		

Statistical analyses

Statistical analysis title	Analysis of Overall Response

Statistical analysis description:

The odds ratio (carfilzomib/bortezomib) was calculated using the Cochran-Mantel-Haenszel method stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration.

Comparison groups	Bortezomib + DEX v Carfilzomib + DEX
Number of subjects included in analysis	929
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Stratified Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.519
upper limit	2.718

Notes:

[5] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.
[6] - Cochran-Mantel-Haenszel test stratified by the randomization 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 an sCR, CR, VGPR, or PR. Duration of response is defined as the time from first evidence of PR or better to confirmation of disease progression or death due to any cause. Median duration of response was estimated using the Kaplan-Meier method. Participants with no baseline disease assessments, starting a new anticancer therapy before documentation of disease progression or death, death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or alive without documentation of disease progression before the data cut-off date were censored. "99999" indicates data that could not be estimated.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 10 November 2014; median follow-up time for DOR was 9.4 and 10.4 months for each treatment group respectively.

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	357		
Units: months				
median (confidence interval 95%)	10.4 (9.3 to 13.8)	21.3 (21.3 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ≥ Grade 2 Peripheral Neuropathy

End point title	Percentage of Participants with ≥ Grade 2 Peripheral Neuropathy

End point description:

Neuropathy events were defined as Grade 2 or higher peripheral neuropathy as specified by peripheral neuropathy Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query, narrow (scope) (SMQN) terms. Peripheral neuropathy was assessed by neurologic exam and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03:
Grade 1: Asymptomatic;
Grade 2: Moderate symptoms, limiting instrumental activities of daily living (ADL)
Grade 3: Severe symptoms; limiting self-care ADL;
Grade 4: Life-threatening consequences, urgent intervention indicated;
Grade 5: Death.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to 30 days after the last dose of study drug as of the data cut-off date of 10 November 2014; median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group.

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	456	463		
Units: percentage of participants				
number (confidence interval 95%)	32.0 (27.7 to 36.3)	6.0 (3.9 to 8.2)		

Statistical analyses

Statistical analysis title	Analysis of Peripheral Neuropathy

Statistical analysis description:

The odds ratio (carfilzomib/bortezomib) was estimated using the unconditional Cochran-Mantel-Haenszel method.

Comparison groups	Bortezomib + DEX v Carfilzomib + DEX
Number of subjects included in analysis	919
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.089
upper limit	0.21

Notes:

[7] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.

Secondary: Percentage of Participants with a Significant Reduction in Left Ventricular Ejection Fraction (LVEF)

End point title	Percentage of Participants with a Significant Reduction in Left Ventricular Ejection Fraction (LVEF)

End point description:

A significant reduction in LVEF was defined as a ≥ 10% decrease (absolute change) from baseline in participants whose baseline LVEF is ≤ 55%.
For participants with LVEF > 55% at baseline, a significant change was defined as a decrease in LVEF to < 45%.
The analysis was based in the cardiopulmonary safety evaluable subgroup (all randomized participants who enrolled in the cardiopulmonary substudy with evaluable baseline echocardiogram scans per the central laboratory) and with both baseline and at least one post-baseline LVEF measurement within 24 weeks.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	48		
Units: percentage of participants				
number (not applicable)	2.6	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Right Ventricular Fractional Area Change (FAC)

End point title	Change from Baseline in Right Ventricular Fractional Area Change (FAC)

End point description:

Right ventricular function was assessed by measuring fractional area change (FAC) on echocardiogram. The analysis was based on the cardiopulmonary safety evaluable subgroup with available FAC data at baseline; "n" indicates participants whose results were available at both the baseline and the specified post-baseline visit.

End point type	Secondary

End point timeframe:

Baseline and Weeks 12, 24 and 36 and at end of treatment (median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group).

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	55		
Units: percent fractional area change				
arithmetic mean (standard deviation)				
Week 12 (n = 40, 40)	-0.7 (± 5.00)	-1.1 (± 5.36)		
Week 24 (n = 26, 31)	0.7 (± 6.10)	-1.0 (± 5.03)		
Week 36 (n = 15, 18)	-0.5 (± 7.27)	-0.5 (± 6.38)		
End of Treatment (n = 23, 18)	0.4 (± 4.73)	-1.9 (± 5.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pulmonary Artery Systolic Pressure (PASP)

End point title	Change from Baseline in Pulmonary Artery Systolic Pressure (PASP)

End point description:

Pulmonary artery pressure was measured using transthoracic echocardiogram.
The analysis was based on the cardiopulmonary safety evaluable subgroup with available PASP data at baseline; "n" indicates participants whose results were available at both the baseline and the specified post-baseline visit.

End point type	Secondary

End point timeframe:

Baseline and Weeks 12, 24 and 36 and at end of treatment (median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group).

End point values	Bortezomib + DEX	Carfilzomib + DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	45		
Units: mmHg				
arithmetic mean (standard deviation)				
Week 12 (n=34, 30)|	0.3 (± 11.72)	2.8 (± 11.44)		
Week 24 (n=22, 20)|	1.7 (± 8.47)	3.4 (± 13.63)		
Week 36 (n=12, 14)|	4.0 (± 7.24)	2.6 (± 13.55)		
End of Treatment (n=21, 14)|	3.4 (± 8.14)	0.9 (± 11.40)		

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 up to 30 days after the last dose of study drug as of the data cut-off date of 20 March 2018; median duration of treatment was 27 weeks in the bortezomib group and 48 weeks in the carfilzomib treatment group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Bortezomib + DEX

Reporting group description:

Participants received bortezomib 1.3 mg/m² administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

Reporting group title	Carfilzomib + DEX

Reporting group description:

Participants received 20 mg/m² carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

Serious adverse events	Bortezomib + DEX	Carfilzomib + DEX	
Total subjects affected by serious adverse events			
subjects affected / exposed	184 / 456 (40.35%)	279 / 463 (60.26%)	
number of deaths (all causes)	261	241	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural neoplasm			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	1 / 456 (0.22%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	1 / 1	3 / 3	
Plasmacytoma			
subjects affected / exposed	0 / 456 (0.00%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic embolus			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arteriosclerosis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 456 (0.66%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 456 (0.88%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	4 / 456 (0.88%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal hernia repair			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy closure			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoid operation			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of internal fixation			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chest pain			
subjects affected / exposed	4 / 456 (0.88%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Disease progression			
subjects affected / exposed	6 / 456 (1.32%)	9 / 463 (1.94%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	3 / 3	5 / 5	
Fatigue			

subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 456 (0.00%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 456 (0.66%)	19 / 463 (4.10%)	
occurrences causally related to treatment / all	1 / 3	10 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	3 / 3	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine haemorrhage			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 456 (0.22%)	18 / 463 (3.89%)	
occurrences causally related to treatment / all	0 / 1	11 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epistaxis			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung disorder			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 456 (0.66%)	10 / 463 (2.16%)	
occurrences causally related to treatment / all	2 / 3	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 456 (0.00%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Confusional state			
subjects affected / exposed	4 / 456 (0.88%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent depressive disorder			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cortisol decreased			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza B virus test positive			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 456 (0.66%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (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	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Hip fracture			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (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	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	2 / 456 (0.44%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 456 (0.88%)	7 / 463 (1.51%)	
occurrences causally related to treatment / all	1 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bifascicular block			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	2 / 2	
Cardiac failure			
subjects affected / exposed	3 / 456 (0.66%)	10 / 463 (2.16%)	
occurrences causally related to treatment / all	1 / 3	6 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure acute			

subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac hypertrophy			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 456 (0.44%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acquired epileptic aphasia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 456 (0.00%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			

subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic coma			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	2 / 456 (0.44%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (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 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	2 / 456 (0.44%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis brachial			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 456 (0.44%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 456 (0.88%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 456 (0.44%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 456 (0.22%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 456 (0.66%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytosis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 456 (1.32%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	3 / 6	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (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 distension			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 456 (0.44%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 456 (0.44%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	11 / 456 (2.41%)	7 / 463 (1.51%)	
occurrences causally related to treatment / all	10 / 12	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 456 (0.44%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	3 / 456 (0.66%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 456 (0.66%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia oral			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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 / 456 (0.44%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 456 (0.44%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatocellular injury			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus generalised			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	7 / 456 (1.54%)	11 / 463 (2.38%)	
occurrences causally related to treatment / all	1 / 7	4 / 13	
deaths causally related to treatment / all	0 / 0	1 / 1	
Albuminuria			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 456 (0.00%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	3 / 456 (0.66%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 456 (0.66%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 456 (0.66%)	6 / 463 (1.30%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 456 (0.44%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 456 (0.44%)	10 / 463 (2.16%)	
occurrences causally related to treatment / all	2 / 2	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 456 (0.22%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 456 (0.00%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomyelitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 456 (0.88%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus sepsis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex encephalitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 456 (0.00%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	5 / 456 (1.10%)	7 / 463 (1.51%)	
occurrences causally related to treatment / all	1 / 6	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 456 (0.66%)	5 / 463 (1.08%)	
occurrences causally related to treatment / all	1 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising ulcerative periodontitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	44 / 456 (9.65%)	49 / 463 (10.58%)	
occurrences causally related to treatment / all	16 / 52	16 / 55	
deaths causally related to treatment / all	2 / 2	3 / 3	
Pneumonia bacterial			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 456 (0.00%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia moraxella			

subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	2 / 456 (0.44%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	5 / 456 (1.10%)	10 / 463 (2.16%)	
occurrences causally related to treatment / all	2 / 5	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	5 / 456 (1.10%)	8 / 463 (1.73%)	
occurrences causally related to treatment / all	2 / 8	1 / 9	
deaths causally related to treatment / all	3 / 3	2 / 2	
Septic shock			
subjects affected / exposed	3 / 456 (0.66%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	2 / 2	3 / 3	
Sinusitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
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	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 456 (0.66%)	8 / 463 (1.73%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 456 (0.88%)	8 / 463 (1.73%)	
occurrences causally related to treatment / all	1 / 5	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 456 (0.66%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Viral infection			

subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 456 (0.44%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 456 (0.66%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 456 (0.44%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 456 (0.22%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	5 / 456 (1.10%)	0 / 463 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 456 (0.22%)	4 / 463 (0.86%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	1 / 456 (0.22%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 456 (0.22%)	3 / 463 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 456 (0.22%)	2 / 463 (0.43%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 456 (0.00%)	1 / 463 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bortezomib + DEX	Carfilzomib + DEX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	435 / 456 (95.39%)	446 / 463 (96.33%)	
Vascular disorders			
Flushing			
subjects affected / exposed	7 / 456 (1.54%)	24 / 463 (5.18%)	
occurrences (all)	13	34	
Hypertension			
subjects affected / exposed	46 / 456 (10.09%)	150 / 463 (32.40%)	
occurrences (all)	71	356	
Hypotension			

subjects affected / exposed	37 / 456 (8.11%)	29 / 463 (6.26%)	
occurrences (all)	50	36	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	79 / 456 (17.32%)	107 / 463 (23.11%)	
occurrences (all)	136	231	
Chest pain			
subjects affected / exposed	19 / 456 (4.17%)	43 / 463 (9.29%)	
occurrences (all)	23	54	
Chills			
subjects affected / exposed	12 / 456 (2.63%)	26 / 463 (5.62%)	
occurrences (all)	15	40	
Fatigue			
subjects affected / exposed	140 / 456 (30.70%)	149 / 463 (32.18%)	
occurrences (all)	304	320	
Influenza like illness			
subjects affected / exposed	10 / 456 (2.19%)	25 / 463 (5.40%)	
occurrences (all)	24	43	
Malaise			
subjects affected / exposed	8 / 456 (1.75%)	24 / 463 (5.18%)	
occurrences (all)	8	66	
Oedema peripheral			
subjects affected / exposed	77 / 456 (16.89%)	98 / 463 (21.17%)	
occurrences (all)	129	167	
Pyrexia			
subjects affected / exposed	68 / 456 (14.91%)	145 / 463 (31.32%)	
occurrences (all)	101	294	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	73 / 456 (16.01%)	127 / 463 (27.43%)	
occurrences (all)	106	201	
Dyspnoea			
subjects affected / exposed	62 / 456 (13.60%)	144 / 463 (31.10%)	
occurrences (all)	87	267	
Epistaxis			

subjects affected / exposed	14 / 456 (3.07%)	24 / 463 (5.18%)	
occurrences (all)	15	31	
Oropharyngeal pain			
subjects affected / exposed	19 / 456 (4.17%)	28 / 463 (6.05%)	
occurrences (all)	23	35	
Productive cough			
subjects affected / exposed	15 / 456 (3.29%)	27 / 463 (5.83%)	
occurrences (all)	22	41	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	33 / 456 (7.24%)	20 / 463 (4.32%)	
occurrences (all)	34	24	
Insomnia			
subjects affected / exposed	122 / 456 (26.75%)	125 / 463 (27.00%)	
occurrences (all)	173	236	
Investigations			
Blood creatinine increased			
subjects affected / exposed	30 / 456 (6.58%)	52 / 463 (11.23%)	
occurrences (all)	48	138	
Creatinine renal clearance decreased			
subjects affected / exposed	19 / 456 (4.17%)	29 / 463 (6.26%)	
occurrences (all)	58	120	
Lymphocyte count decreased			
subjects affected / exposed	18 / 456 (3.95%)	42 / 463 (9.07%)	
occurrences (all)	126	372	
Platelet count decreased			
subjects affected / exposed	41 / 456 (8.99%)	58 / 463 (12.53%)	
occurrences (all)	177	288	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	25 / 456 (5.48%)	20 / 463 (4.32%)	
occurrences (all)	29	30	
Fall			
subjects affected / exposed	25 / 456 (5.48%)	19 / 463 (4.10%)	
occurrences (all)	32	32	
Nervous system disorders			

Dizziness			
subjects affected / exposed	69 / 456 (15.13%)	42 / 463 (9.07%)	
occurrences (all)	111	59	
Dysgeusia			
subjects affected / exposed	27 / 456 (5.92%)	17 / 463 (3.67%)	
occurrences (all)	30	19	
Headache			
subjects affected / exposed	49 / 456 (10.75%)	97 / 463 (20.95%)	
occurrences (all)	77	179	
Hypoaesthesia			
subjects affected / exposed	14 / 456 (3.07%)	24 / 463 (5.18%)	
occurrences (all)	21	46	
Neuralgia			
subjects affected / exposed	72 / 456 (15.79%)	11 / 463 (2.38%)	
occurrences (all)	123	23	
Neuropathy peripheral			
subjects affected / exposed	130 / 456 (28.51%)	49 / 463 (10.58%)	
occurrences (all)	276	74	
Paraesthesia			
subjects affected / exposed	76 / 456 (16.67%)	43 / 463 (9.29%)	
occurrences (all)	169	60	
Peripheral sensory neuropathy			
subjects affected / exposed	70 / 456 (15.35%)	29 / 463 (6.26%)	
occurrences (all)	150	56	
Polyneuropathy			
subjects affected / exposed	27 / 456 (5.92%)	6 / 463 (1.30%)	
occurrences (all)	60	7	
Tremor			
subjects affected / exposed	23 / 456 (5.04%)	10 / 463 (2.16%)	
occurrences (all)	28	13	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	131 / 456 (28.73%)	201 / 463 (43.41%)	
occurrences (all)	352	722	
Lymphopenia			

subjects affected / exposed	25 / 456 (5.48%)	31 / 463 (6.70%)	
occurrences (all)	109	207	
Neutropenia			
subjects affected / exposed	26 / 456 (5.70%)	28 / 463 (6.05%)	
occurrences (all)	49	94	
Thrombocytopenia			
subjects affected / exposed	83 / 456 (18.20%)	100 / 463 (21.60%)	
occurrences (all)	241	483	
Eye disorders			
Cataract			
subjects affected / exposed	20 / 456 (4.39%)	36 / 463 (7.78%)	
occurrences (all)	25	43	
Vision blurred			
subjects affected / exposed	23 / 456 (5.04%)	23 / 463 (4.97%)	
occurrences (all)	24	31	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	26 / 456 (5.70%)	20 / 463 (4.32%)	
occurrences (all)	44	22	
Abdominal pain			
subjects affected / exposed	38 / 456 (8.33%)	32 / 463 (6.91%)	
occurrences (all)	58	48	
Abdominal pain upper			
subjects affected / exposed	35 / 456 (7.68%)	24 / 463 (5.18%)	
occurrences (all)	50	29	
Constipation			
subjects affected / exposed	127 / 456 (27.85%)	75 / 463 (16.20%)	
occurrences (all)	196	100	
Diarrhoea			
subjects affected / exposed	184 / 456 (40.35%)	169 / 463 (36.50%)	
occurrences (all)	423	353	
Dyspepsia			
subjects affected / exposed	25 / 456 (5.48%)	36 / 463 (7.78%)	
occurrences (all)	31	46	
Nausea			

subjects affected / exposed	90 / 456 (19.74%)	109 / 463 (23.54%)	
occurrences (all)	128	194	
Vomiting			
subjects affected / exposed	45 / 456 (9.87%)	77 / 463 (16.63%)	
occurrences (all)	62	157	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	29 / 456 (6.36%)	34 / 463 (7.34%)	
occurrences (all)	36	54	
Rash			
subjects affected / exposed	35 / 456 (7.68%)	42 / 463 (9.07%)	
occurrences (all)	45	63	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	51 / 456 (11.18%)	61 / 463 (13.17%)	
occurrences (all)	71	79	
Bone pain			
subjects affected / exposed	41 / 456 (8.99%)	50 / 463 (10.80%)	
occurrences (all)	78	93	
Back pain			
subjects affected / exposed	81 / 456 (17.76%)	106 / 463 (22.89%)	
occurrences (all)	114	148	
Muscle spasms			
subjects affected / exposed	28 / 456 (6.14%)	93 / 463 (20.09%)	
occurrences (all)	39	158	
Muscular weakness			
subjects affected / exposed	47 / 456 (10.31%)	44 / 463 (9.50%)	
occurrences (all)	68	69	
Musculoskeletal chest pain			
subjects affected / exposed	20 / 456 (4.39%)	39 / 463 (8.42%)	
occurrences (all)	25	51	
Musculoskeletal pain			
subjects affected / exposed	25 / 456 (5.48%)	27 / 463 (5.83%)	
occurrences (all)	29	33	
Myalgia			

subjects affected / exposed	19 / 456 (4.17%)	29 / 463 (6.26%)	
occurrences (all)	34	39	
Pain in extremity			
subjects affected / exposed	50 / 456 (10.96%)	55 / 463 (11.88%)	
occurrences (all)	96	81	
Infections and infestations			
Bronchitis			
subjects affected / exposed	45 / 456 (9.87%)	103 / 463 (22.25%)	
occurrences (all)	78	162	
Conjunctivitis			
subjects affected / exposed	37 / 456 (8.11%)	23 / 463 (4.97%)	
occurrences (all)	49	30	
Nasopharyngitis			
subjects affected / exposed	59 / 456 (12.94%)	79 / 463 (17.06%)	
occurrences (all)	95	162	
Pneumonia			
subjects affected / exposed	22 / 456 (4.82%)	32 / 463 (6.91%)	
occurrences (all)	25	40	
Respiratory tract infection			
subjects affected / exposed	32 / 456 (7.02%)	47 / 463 (10.15%)	
occurrences (all)	45	92	
Rhinitis			
subjects affected / exposed	10 / 456 (2.19%)	30 / 463 (6.48%)	
occurrences (all)	15	45	
Upper respiratory tract infection			
subjects affected / exposed	80 / 456 (17.54%)	117 / 463 (25.27%)	
occurrences (all)	135	247	
Urinary tract infection			
subjects affected / exposed	29 / 456 (6.36%)	36 / 463 (7.78%)	
occurrences (all)	43	47	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 456 (13.82%)	51 / 463 (11.02%)	
occurrences (all)	85	62	
Hyperuricaemia			

subjects affected / exposed	8 / 456 (1.75%)	31 / 463 (6.70%)	
occurrences (all)	11	58	
Hyperglycaemia			
subjects affected / exposed	43 / 456 (9.43%)	53 / 463 (11.45%)	
occurrences (all)	77	140	
Hypocalcaemia			
subjects affected / exposed	19 / 456 (4.17%)	29 / 463 (6.26%)	
occurrences (all)	23	38	
Hypokalaemia			
subjects affected / exposed	51 / 456 (11.18%)	64 / 463 (13.82%)	
occurrences (all)	87	95	
Hypophosphataemia			
subjects affected / exposed	28 / 456 (6.14%)	33 / 463 (7.13%)	
occurrences (all)	56	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2012	The main purpose of this amendment was to incorporate the changes from the carfilzomib Investigator's Brochure, Version 11.0 (dated 22 August 2012). Updated text of importance was included in the background information regarding relevant Phase 1 and 2 carfilzomib studies; safety and efficacy text due the carfilzomib marketing approval by the US FDA (July 2012). This amendment also included the addition of assessments for the cardiac and pulmonary substudy safety monitoring, as specified in the study objectives, as follows: • Right ventricular (RV) function, RV size, RV wall thickness; and • Pulmonary artery pressure in all subjects at baseline as well as every 12 weeks, and at the end of study for those subjects who participate in the echocardiogram substudy. The following exploratory objectives were added: • Evaluate PK/PDn relationships for safety and efficacy. • Analyze genetic and gene expression biomarkers that may potentially predict for response and resistance following treatment with proteasome inhibitors from all subjects who consent to optional genomic biomarker analysis. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency.
02 October 2014	The main purpose of this amendment was to specify that the Global Health Status/QoL Scale (measured by EORTC) subscale was to be analyzed as a secondary endpoint and that other subscales were to be analyzed as exploratory endpoints (EORTC QLQ-C30, QLQ-MY20, FACT-GOG/Ntx, and MRU). Additional major changes included the following: • Added the MRD status exploratory endpoint. • Specified the timing and details regarding bone marrow aspirate samples that were to be collected as part of the optional MRD analysis. • Clarified procedures for survival follow-up in order to collect OS data using ad hoc survival sweeps • Clarified that plasma concentrations of carfilzomib, along with other potential excipients, were to be determined as needed based on carfilzomib PK data analysis. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency. There were no changes to inclusion/exclusion criteria based on this amendment.
09 January 2015	The main purpose of this amendment was to specify that the number of OS events to study end was changed from 631 to 496, the number of interim analyses for OS was changed from 1 to 2, and the selected landmarks for estimating survival rate were changed from "6 months, 9 months, and 1 year" to "1 year, 2 years, and 3 years" from randomization. Additional major changes included the following: • Changes in statistical analyses of secondary endpoints resulting from changes in final number of OS events were included as necessary. • The Global Health Status/QoL subscale (measured by EORTC QLQ-C30) was moved from a secondary endpoint to an exploratory endpoint • The FACT/GOG-Ntx questionnaire score was removed from the definition of neuropathy events and the joint model. The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency.

30 October 2015	The main purpose of this amendment was to specify the following changes to the study conduct since the primary objective for this study was met: • clarified that subjects who stopped investigational product before progression were to be followed for OS • After the primary objective for this study was met, the following assessments were removed: central lab disease assessments and IRC review for PFS, QoL questionnaires (FACT/GOG-Ntx, EORTC QLQ-C30, QLQ-MY20, and MRU questions), and optional MRD assessments as the centralized disease assessments was removed Additional major changes included the following: • updated guidelines for treatment-emergent toxicities • updated pregnancy reporting timeframe
20 September 2016	The main purpose of this amendment was to explicitly allow subjects to remain on investigational product for a minimum of 3 years or until disease progression, physician decision, unacceptable toxicity, withdrawal of consent, or mortality (whichever occurs first). The time point for completion of at least 3 years treatment and safety follow-up for all subjects who remain on treatment may occur later than the time point wherein OS reaches statistical significance or the final OS analysis occurs. Additional major changes included the following: • recommended actions for posterior reversible encephalopathy syndrome and thrombotic microangiopathy to align with the current Company Core Safety Information • reinserted a (non-critical) paragraph into the statistical methods and analyses section of the protocol synopsis that was mistakenly deleted during drafting of Protocol Amendment 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported