Clinical trial results:
A Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma

Summary

EudraCT number	2009-016840-38
Trial protocol	AT HU CZ ES IT GB SE SK GR DE BE
Global end of trial date	03 November 2015

Results information

Result version number	v1 (current)
This version publication date	19 September 2016
First version publication date	19 September 2016

Trial information

Trial identification

Sponsor protocol code	PX-171-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01302392
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen Study ID: 20130396

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	10 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 3, randomized, open-label, multicenter study comparing two treatment regimens for subjects with multiple myeloma who have received all available approved treatment options and may therefore be considered candidates for palliative care.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Slovakia: 2

Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	315
EEA total number of subjects	266

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)	151
From 65 to 84 years	163
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 06 September 2010 to 21 October 2012. Results are reported as of the data cut-off date of 10 Jul 2014.

Pre-assignment

Screening details:

Eligible subjects were randomized in a 1:1 ratio to carfilzomib or best supportive care. Randomization was stratified based on the number of previous therapies (3 versus 4 versus ≥ 5) and geographical region (Europe versus non-Europe).

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	Best Supportive Care

Arm description:

Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.

Arm type	Active comparator
Investigational medicinal product name	Corticosteriod
Investigational medicinal product code	
Other name	prednisolone, dexamethasone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Either prednisolone 30 mg every other day, dexamethasone 6 mg every other day, or equivalent corticosteroid regimen

Arm title	Carfilzomib

Arm description:

Subjects received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).

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

Dosage and administration details:

Administered by intravenous infusion 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycle 2 through Cycle 9. From cycle 10, 27 mg/m² (or at the last dose given in Cycle 9) IV on Days 1, 2, 15, and 16 (omitting Days 8 and 9) unless the Investigator chose to reinstate the dosing frequency to the original regimen (Days 1, 2, 8, 9, 15,16) for individual patients.

Number of subjects in period 1	Best Supportive Care	Carfilzomib
Started	158	157
Treated	153	157
Completed	151	156
Not completed	7	1
Consent withdrawn by subject	6	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Best Supportive Care
Reporting group description:	
Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.	
Reporting group title	Carfilzomib
Reporting group description:	
Subjects received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).	

Reporting group values	Best Supportive Care	Carfilzomib	Total
Number of subjects	158	157	315
Age categorical Units: Subjects			
< 65 years	83	68	151
≥ 65 years	75	89	164
Age Continuous Units: years			
arithmetic mean	65.5	63.3	
standard deviation	± 8.02	± 10.71	-
Gender, Male/Female Units: participants			
Female	62	75	137
Male	96	82	178
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	1	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	148	151	299
Other	5	4	9
Region Units: Subjects			
Europe	138	140	278
Non-Europe	20	17	37
Number of Prior Regimens to Treat Multiple Myeloma Units: Subjects			
3 regimens	19	17	36
4 regimens	35	34	69
≥ 5 regimens	104	106	210

End points

End points reporting groups

Reporting group title	Best Supportive Care

Reporting group description:

Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.

Reporting group title	Carfilzomib

Reporting group description:

Subjects received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).

Primary: Overall Survival

End point title	Overall Survival

End point description:

Time elapsed between the randomization date and the date of death. Participants who were still alive were censored at the date when the subject was last known alive or the data cutoff date, whichever occurred earlier.

End point type	Primary

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 45 months. Median follow up times were 27.8 months and 29.8 months for Carfilzomib and Best Supportive Care groups, respectively.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: months				
median (confidence interval 95%)	10 (7.7 to 12)	10.2 (8.4 to 14.4)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival
Comparison groups	Best Supportive Care v Carfilzomib

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4172 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.975
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.249

Notes:

[1] - P value was from stratified log-rank test with number of previous therapies (3 versus 4 versus ≥ 5) and geographical region (Europe versus non-Europe) as stratification factors.

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

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

End point type	Secondary

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: months				
median (confidence interval 95%)	3.3 (2.2 to 5.2)	3.7 (2.8 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

End point title	Overall Response

End point description:

Number of participants who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as their best response. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC).

End point type	Secondary

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: participants				
number (not applicable)	18	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was calculated for subjects who achieved a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). Duration of response was defined as the time in months from the initial start of response (PR or better) to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for progression-free survival.
"99999" indicates not calculable due to a low number of participants reaching PD or all-cause death.

End point type	Secondary

End point timeframe:

From the time achieving response through the final analysis data cutoff with longest follow-up time of approximately 29 months.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	30		
Units: months				
median (confidence interval 95%)	9.5 (3.7 to 99999)	7.2 (4.6 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response

End point title	Clinical Benefit Response

End point description:

Number of participants who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), or minimal response (MR) as their best response. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC). (MR was determined using European Group for Blood and Marrow Transplantation criteria)

End point type	Secondary

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: participants				
number (not applicable)	33	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Clinical Benefit

End point title	Duration of Clinical Benefit

End point description:

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

End point type	Secondary

End point timeframe:

From time of achieving clinical benefit through the final analysis data cutoff with longest follow-up time of approximately 30 months.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	49		
Units: months				
median (confidence interval 95%)	8.3 (6.5 to 12.9)	6.4 (4.9 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control

End point title	Disease Control

End point description:

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

End point type	Secondary

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	157		
Units: participants				
number (not applicable)	107	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

Duration of Disease Control was calculated for subjects who achieved disease control. Duration of Disease Control was defined as the time in months from randomization to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for progression-free survival.

End point type	Secondary

End point timeframe:

From time of achieving disease control through the final analysis data cutoff with longest follow-up time of approximately 31 months.

End point values	Best Supportive Care	Carfilzomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	119		
Units: months				
median (confidence interval 95%)	6.6 (5.4 to 8.8)	5.5 (3.9 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization through the final analysis data cutoff with range of follow-up time of 0.4 - 138.3 weeks with median of 10.7 weeks in Best Supportive Care arm, and 0.3 - 138.4 weeks with median of 16.3 weeks in carfilzomib arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Carfilzomib

Reporting group description:

Participants received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).

Reporting group title	Best Supportive Care

Reporting group description:

Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.

Serious adverse events	Carfilzomib	Best Supportive Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 157 (58.60%)	78 / 153 (50.98%)	
number of deaths (all causes)	129	123	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic neoplasm malignant			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia plasmacytic			

subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (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	0 / 157 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Disease progression			
subjects affected / exposed	16 / 157 (10.19%)	19 / 153 (12.42%)	
occurrences causally related to treatment / all	0 / 16	0 / 19	
deaths causally related to treatment / all	0 / 14	0 / 14	
General physical health deterioration			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pain			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 157 (3.82%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	3 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
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 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	2 / 157 (1.27%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory failure			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (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	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	2 / 157 (1.27%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac failure			
subjects affected / exposed	4 / 157 (2.55%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 157 (1.27%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 157 (1.27%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 157 (2.55%)	8 / 153 (5.23%)	
occurrences causally related to treatment / all	1 / 6	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 157 (1.91%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 157 (0.64%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 157 (1.91%)	5 / 153 (3.27%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (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	1 / 157 (0.64%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 157 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (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	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 157 (1.91%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	15 / 157 (9.55%)	6 / 153 (3.92%)	
occurrences causally related to treatment / all	1 / 15	2 / 7	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	6 / 157 (3.82%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 157 (0.64%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint effusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 157 (1.27%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (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	2 / 157 (1.27%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Bacteraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 157 (1.91%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	6 / 157 (3.82%)	5 / 153 (3.27%)	
occurrences causally related to treatment / all	1 / 6	2 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 157 (0.64%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasopharyngitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 157 (6.37%)	18 / 153 (11.76%)	
occurrences causally related to treatment / all	3 / 11	5 / 22	
deaths causally related to treatment / all	0 / 1	2 / 7	
Pneumonia pneumococcal			

subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 157 (1.91%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 157 (0.64%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 157 (0.00%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Staphylococcal sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	3 / 157 (1.91%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	7 / 157 (4.46%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	1 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 157 (0.64%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 153 (0.65%)	
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	3 / 157 (1.91%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Carfilzomib	Best Supportive Care	
Total subjects affected by non-serious adverse events subjects affected / exposed	141 / 157 (89.81%)	135 / 153 (88.24%)	
Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	9 / 157 (5.73%)	4 / 153 (2.61%)	
occurrences (all)	23	6	
Blood creatinine increased			
subjects affected / exposed	13 / 157 (8.28%)	10 / 153 (6.54%)	
occurrences (all)	21	15	
Neutrophil count decreased			
subjects affected / exposed	13 / 157 (8.28%)	10 / 153 (6.54%)	
occurrences (all)	21	19	
Platelet count decreased			
subjects affected / exposed	12 / 157 (7.64%)	12 / 153 (7.84%)	
occurrences (all)	33	20	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 157 (14.65%)	9 / 153 (5.88%)	
occurrences (all)	31	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 157 (6.37%)	3 / 153 (1.96%)	
occurrences (all)	21	4	
Headache			
subjects affected / exposed	17 / 157 (10.83%)	6 / 153 (3.92%)	
occurrences (all)	23	8	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	9 / 157 (5.73%)	15 / 153 (9.80%)	
occurrences (all)	37	48	
Neutropenia			
subjects affected / exposed	22 / 157 (14.01%)	23 / 153 (15.03%)	
occurrences (all)	73	45	
Anaemia			
subjects affected / exposed	88 / 157 (56.05%)	72 / 153 (47.06%)	
occurrences (all)	275	212	

Thrombocytopenia			
subjects affected / exposed	58 / 157 (36.94%)	43 / 153 (28.10%)	
occurrences (all)	231	102	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 157 (16.56%)	20 / 153 (13.07%)	
occurrences (all)	44	27	
Chest pain			
subjects affected / exposed	5 / 157 (3.18%)	8 / 153 (5.23%)	
occurrences (all)	6	8	
Chills			
subjects affected / exposed	8 / 157 (5.10%)	1 / 153 (0.65%)	
occurrences (all)	11	1	
Fatigue			
subjects affected / exposed	29 / 157 (18.47%)	28 / 153 (18.30%)	
occurrences (all)	55	46	
Oedema peripheral			
subjects affected / exposed	17 / 157 (10.83%)	12 / 153 (7.84%)	
occurrences (all)	22	14	
Pain			
subjects affected / exposed	8 / 157 (5.10%)	1 / 153 (0.65%)	
occurrences (all)	11	2	
Pyrexia			
subjects affected / exposed	41 / 157 (26.11%)	28 / 153 (18.30%)	
occurrences (all)	92	34	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 157 (6.37%)	20 / 153 (13.07%)	
occurrences (all)	14	22	
Diarrhoea			
subjects affected / exposed	23 / 157 (14.65%)	18 / 153 (11.76%)	
occurrences (all)	37	19	
Dyspepsia			
subjects affected / exposed	10 / 157 (6.37%)	4 / 153 (2.61%)	
occurrences (all)	12	5	
Vomiting			

subjects affected / exposed	15 / 157 (9.55%)	5 / 153 (3.27%)	
occurrences (all)	25	6	
Nausea			
subjects affected / exposed	31 / 157 (19.75%)	14 / 153 (9.15%)	
occurrences (all)	50	15	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	12 / 157 (7.64%)	10 / 153 (6.54%)	
occurrences (all)	17	20	
Dyspnoea			
subjects affected / exposed	21 / 157 (13.38%)	12 / 153 (7.84%)	
occurrences (all)	36	12	
Cough			
subjects affected / exposed	19 / 157 (12.10%)	10 / 153 (6.54%)	
occurrences (all)	27	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 157 (2.55%)	18 / 153 (11.76%)	
occurrences (all)	4	22	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	8 / 157 (5.10%)	3 / 153 (1.96%)	
occurrences (all)	8	5	
Renal impairment			
subjects affected / exposed	11 / 157 (7.01%)	5 / 153 (3.27%)	
occurrences (all)	33	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 157 (7.01%)	6 / 153 (3.92%)	
occurrences (all)	14	8	
Back pain			
subjects affected / exposed	13 / 157 (8.28%)	16 / 153 (10.46%)	
occurrences (all)	15	23	
Bone pain			
subjects affected / exposed	18 / 157 (11.46%)	16 / 153 (10.46%)	
occurrences (all)	25	20	

Pain in extremity			
subjects affected / exposed	13 / 157 (8.28%)	7 / 153 (4.58%)	
occurrences (all)	16	7	
Musculoskeletal pain			
subjects affected / exposed	5 / 157 (3.18%)	10 / 153 (6.54%)	
occurrences (all)	6	12	
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 157 (8.28%)	13 / 153 (8.50%)	
occurrences (all)	22	14	
Nasopharyngitis			
subjects affected / exposed	13 / 157 (8.28%)	10 / 153 (6.54%)	
occurrences (all)	23	14	
Respiratory tract infection			
subjects affected / exposed	10 / 157 (6.37%)	6 / 153 (3.92%)	
occurrences (all)	14	7	
Upper respiratory tract infection			
subjects affected / exposed	16 / 157 (10.19%)	3 / 153 (1.96%)	
occurrences (all)	26	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 157 (5.73%)	7 / 153 (4.58%)	
occurrences (all)	10	9	
Hypercalcaemia			
subjects affected / exposed	13 / 157 (8.28%)	9 / 153 (5.88%)	
occurrences (all)	25	14	
Hyperglycaemia			
subjects affected / exposed	6 / 157 (3.82%)	8 / 153 (5.23%)	
occurrences (all)	10	14	
Hyperkalaemia			
subjects affected / exposed	8 / 157 (5.10%)	2 / 153 (1.31%)	
occurrences (all)	14	2	
Hyperuricaemia			
subjects affected / exposed	19 / 157 (12.10%)	10 / 153 (6.54%)	
occurrences (all)	20	16	
Hypocalcaemia			

subjects affected / exposed	11 / 157 (7.01%)	10 / 153 (6.54%)	
occurrences (all)	20	15	
Hypokalaemia			
subjects affected / exposed	14 / 157 (8.92%)	13 / 153 (8.50%)	
occurrences (all)	25	16	
Hypomagnesaemia			
subjects affected / exposed	11 / 157 (7.01%)	11 / 153 (7.19%)	
occurrences (all)	23	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2011	1) In order to adhere to CHMP guidance to design a study with survival as the primary endpoint, the primary endpoint was changed from PFS to OS. This was accompanied by an increase in sample size from 84 to 302 in order to provide 80% power to detect a 43% increase in OS for carfilzomib over control. A regional stratification variable was added to control for the additional sites and countries that were added for the increased sample size. 2) The window provided in Inclusion Criterion 2 to demonstrate measurable disease by central laboratory analysis of M-proteins was increased from 14 days originally to 21 days in order to account for the challenges in logistics of trans-country sample shipment followed by analysis and review.
08 March 2012	1) The interim analysis at 50% of the total number of OS events was removed, and the interim analysis of OS at approximately 75% of the total number of OS events was retained to ensure that the data were mature at the time of the interim analysis and to adhere to CHMP guidance. 2) Inclusion Criterion 11, which required prior treatment with anthracycline, was eliminated in order to expand study access to subjects being managed per current standard of care which does not support the routine use of anthracyclines. 3) Exclusion Criterion 21, which excluded subjects with any contraindications to the required concomitant drugs or supportive treatments, was added to ensure subject safety.
11 February 2013	1) Since OS was the primary endpoint, the study was amended to remove the requirement of response and progression assessments by an Independent Review Committee and instead to specify that the investigator's assessment of response and progression was to be used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported