



Clinical trial results:

A Randomized, Open-label, Phase 3 Study in Subjects With Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination With Dexamethasone, Comparing Once-weekly Versus Twice-weekly Carfilzomib Dosing

Summary

EudraCT number	2014-005325-12
Trial protocol	GB DE IT HU BE DK ES PL GR SE FI RO
Global end of trial date	07 January 2019

Results information

Result version number	v2 (current)
This version publication date	22 December 2019
First version publication date	28 December 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CFZ014
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02412878
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen Study ID: 20140355

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the progression-free survival (PFS) of once-weekly carfilzomib dosing in combination with dexamethasone to the PFS of twice-weekly carfilzomib dosing in combination with dexamethasone in subjects with relapsed and refractory multiple myeloma who have received prior treatment with a proteasome inhibitor and an immunomodulatory agent.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH), Good Clinical Practice (GCP) regulations/guidelines.

The protocol, protocol amendments, and proposed informed consent form were submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval. A copy of the written approval of the protocol, amendments, and informed consent form was received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	19 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Greece: 46
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Italy: 65
Country: Number of subjects enrolled	Norway: 2

Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	478
EEA total number of subjects	395

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)	208
From 65 to 84 years	269
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from September 2015 to August 2016 at 118 sites in Australia, New Zealand, Japan, North America, and Europe.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to receive a regimen consisting of either once-weekly or twice weekly carfilzomib in combination with dexamethasone.

Randomization was stratified by International Staging System (ISS) stage (stage 1 vs stages 2 or 3), refractory to bortezomib treatment (yes vs no), and age (< 65 vs ≥ 65 years).

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	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone

Arm description:

Participants received carfilzomib administered by intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 of cycle 1 and 27 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	PR-171
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib was administered as an IV infusion 20/27 mg/m² twice-weekly

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

Dosage and administration details:

40 mg dexamethasone IV or orally.

Arm title	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
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Arm description:

Participants received carfilzomib administered by IV infusion on days 1, 8, and 15 of each 28-day cycle (20 mg/m² on day 1 of cycle 1 and 70 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Arm type	Experimental
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Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	PR-171
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib was administered as an IV infusion 20/27 mg/m² once-weekly

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

Dosage and administration details:

40 mg dexamethasone IV or orally.

Number of subjects in period 1	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Started	238	240
Received Carfilzomib	235	238
Completed	217	227
Not completed	21	13
Consent withdrawn by subject	19	10
Lost to follow-up	2	3

Baseline characteristics

Reporting groups

Reporting group title	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone
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Reporting group description:

Participants received carfilzomib administered by intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 of cycle 1 and 27 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Reporting group title	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
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Reporting group description:

Participants received carfilzomib administered by IV infusion on days 1, 8, and 15 of each 28-day cycle (20 mg/m² on day 1 of cycle 1 and 70 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Reporting group values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone	Total
Number of subjects	238	240	478
Age, Customized			
Units: Subjects			
18 - 64 years	104	104	208
65 - 74 years	102	90	192
75 - 84 years	32	45	77
≥ 85 years	0	1	1
Age Continuous			
Units: years			
median	66.0	66.0	
full range (min-max)	35 to 83	39 to 85	-
Sex: Female, Male			
Units: Subjects			
Female	110	108	218
Male	128	132	260
Race/Ethnicity, Customized			
Units: Subjects			
Asian	15	30	45
Black or African American	2	3	5
White	202	200	402
Other	9	4	13
Missing	10	3	13
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	2	7
Not Hispanic or Latino	226	235	461
Unknown or Not Reported	7	3	10
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about >			

50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	118	118	236
1 (Restrictive but ambulatory)	120	121	241
2 (Ambulatory but unable to work)	0	1	1
Stratification Factor: International Staging System (ISS) stage			
The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group: • Stage I: $\beta 2$ -microglobulin ($\beta 2M$) < 3.5 mg/L, albumin \geq 3.5 g/dL • Stage II: $\beta 2M$ < 3.5 mg/L and albumin < 3.5 g/dL; or $\beta 2M$ 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin • Stage III: $\beta 2M \geq$ 5.5 mg/L			
Units: Subjects			
Stage 1	100	100	200
Stage 2 or 3	138	140	278
Stratification Factor: Refractory to Bortezomib Treatment			
Participants were classified as refractory to bortezomib in prior regimens if the data collected on prior multiple myeloma therapy indicated that any of the following criteria were met: a. Best Response to any regimen containing bortezomib was stable disease or progressive disease. b. Reason bortezomib was stopped was progression in any regimen. c. Date of relapse/progression was after start date and within 60 days after stop date of bortezomib in any regimen.			
Units: Subjects			
Yes	88	88	176
No	150	152	302

End points

End points reporting groups

Reporting group title	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone
Reporting group description: Participants received carfilzomib administered by intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m ² on days 1 and 2 of cycle 1 and 27 mg/m ² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.	
Reporting group title	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Reporting group description: Participants received carfilzomib administered by IV infusion on days 1, 8, and 15 of each 28-day cycle (20 mg/m ² on day 1 of cycle 1 and 70 mg/m ² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.	

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. Disease status was assessed at a central laboratory with serum and urine protein electrophoresis, immunofixation, serum-free light chain (SFLC) assay, bone marrow sample evaluation, serum calcium, plasmacytoma evaluation, and skeletal survey. Response and disease progression were determined using a validated computer algorithm based on the International Myeloma Working Group—Uniform Response Criteria (IMWG-URC). Median PFS was derived using the Kaplan-Meier method; participants still alive with no disease progression were censored at the time of their last disease assessment.	
End point type	Primary
End point timeframe: From randomization until the data cut-off date of 15 June 2017; median (minimum, maximum) follow-up time for PFS was 12.0 (0, 20) and 12.6 (0, 19) months in each treatment group respectively.	

End point values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: months				
median (confidence interval 95%)	7.6 (5.8 to 9.2)	11.2 (8.6 to 13.0)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: The inferential comparison between the 2 treatment groups used the 1-sided log-rank test stratified by	

the randomization stratification factors. A 1-sided p-value was compared against the prespecified adjusted alpha value of 0.011 to determine significance.

The hazard ratio (once weekly carfilzomib 20/70 mg/m²/ twice weekly carfilzomib 20/27 mg/m²) was estimated from a stratified Cox proportional hazards model.

Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0014 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.693
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	0.883

Notes:

[1] - To ensure proper control of type I error, analysis of PFS was performed under a group sequential design framework with stopping boundaries constructed using the Lan-DeMets spending function with an O'Brien-Fleming approach.

Progression-free survival, overall response rate, and overall survival were tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate below one-sided 0.025 level.

[2] - One-sided stratified log-rank test, stratified by the randomization factors (ISS stage at study entry, refractory to bortezomib treatment, and age).

Statistical analysis title	Unstratified Analysis
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Statistical analysis description:

The hazard ratio (once weekly carfilzomib 20/70 mg/m²/ twice weekly carfilzomib 20/27 mg/m²) was estimated using an unstratified Cox proportional hazards model.

Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.567
upper limit	0.913

Notes:

[3] - One-sided unstratified log-rank test

Secondary: Overall Response Rate

End point title	Overall Response Rate
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End point description:

Disease response was evaluated according to the IMWG-URC using a validated computer algorithm. Overall response rate was defined as the percentage of participants with a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

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 $\geq 90\%$ reduction in serum M-protein with urine M-protein <100 mg/24 hours. A $\geq 50\%$ reduction in the size of soft tissue plasmacytomas if present at baseline.

PR: $\geq 50\%$ reduction of serum M-protein and reduction in urine M-protein by $\geq 90\%$ or to < 200 mg/24 hours. A $\geq 50\%$ reduction in the size of soft tissue plasmacytomas if present at baseline.

End point type	Secondary
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End point timeframe:

Disease response was assessed every 28 days until progressive disease, up to the data cut-off date of 15 June 2017; median time on follow-up was 12.0 and 12.6 months in each treatment group respectively.

End point values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: percentage of participants				
number (confidence interval 95%)	40.8 (34.5 to 47.3)	62.9 (56.5 to 69.0)		

Statistical analyses

Statistical analysis title	Primary Analysis
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Statistical analysis description:

The inferential comparison of ORR between treatment groups was performed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. A 1-sided p-value from the test was compared against the prespecified alpha value of 0.021 to determine the significance.

The odds ratio (once weekly carfilzomib 20/70 mg/m²/ twice weekly carfilzomib 20/27 mg/m²) was calculated using the Mantel-Haenszel method stratified by the randomization stratification factors.

Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001 ^[5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.485
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.716
upper limit	3.598

Notes:

[4] - Progression-free survival, overall response, and overall survival were tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate below one-sided 0.025 level.

[5] - One-sided p-value from CMH test stratified by the randomization factors (ISS stage at study entry, refractory to bortezomib treatment, and age).

Statistical analysis title	Unstratified Analysis
Statistical analysis description: The odds ratio (once weekly carfilzomib 20/70 mg/m ² / twice weekly carfilzomib 20/27 mg/m ²) was calculated using the Mantel-Haenszel method.	
Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.466
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.707
upper limit	3.563

Secondary: Overall Survival

End point title	Overall Survival
End point description: Overall Survival (OS) was defined as the time from randomization to death due to any cause. Median overall survival was derived using the Kaplan-Meier method; participants still alive were censored at the date last known to be alive. "99999" indicates values that could not be estimated due to the low number of events at the time of the analysis.	
End point type	Secondary
End point timeframe: From randomization until the data cut-off date of 15 June 2017; median (minimum, maximum) follow-up time for OS was 12.6 (0, 20) and 13.2 (0, 19) months in each treatment group respectively.	

End point values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	240		
Units: months				
median (confidence interval 95%)	99999 (18.1 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The inferential comparison between the 2 treatment groups for OS used the 1-sided log-rank test stratified by the randomization stratification factors. A 1-sided p-value was compared against the prespecified adjusted alpha value of 0.018 to determine significance. The hazard ratio (once weekly carfilzomib 20/70 mg/m ² / twice weekly carfilzomib 20/27 mg/m ²) was estimated using a Cox proportional hazards model stratified by the randomization stratification factors.	
Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.107 ^[7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.563
upper limit	1.138

Notes:

[6] - Progression-free survival, overall response, and overall survival were tested using a fixed sequence hierarchical testing procedure to control the family-wise type I error rate below one-sided 0.025 level.

[7] - One-sided stratified log-rank test, stratified by the randomization factors (ISS stage at study entry, refractory to bortezomib treatment, and age).

Statistical analysis title	Unstratified Analysis
Statistical analysis description:	
The hazard ratio (once weekly carfilzomib 20/70 mg/m ² / twice weekly carfilzomib 20/27 mg/m ²) was estimated using an unstratified Cox proportional hazards model.	
Comparison groups	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone v Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1326 ^[8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.578
upper limit	1.164

Notes:

[8] - One-sided unstratified log-rank test

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)
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End point description:

The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, where Grade 1 = Mild; Grade

2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening; Grade 5 = Fatal. Treatment-related adverse events are adverse events considered related to at least 1 investigational product by the investigator, including those with unknown relationship.

The safety population included all participants who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
From first dose of study drug up to 30 days after last dose, up to the end of study; median (minimum, maximum) duration of treatment was 29.1 (0.1, 156.3) weeks and 38.0 (0.1, 158.3) weeks in each treatment group respectively.	

End point values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethason e	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethason e		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	238		
Units: participants				
Adverse events (AEs)	230	233		
Adverse events Grade ≥ 3	152	181		
Serious adverse events	102	118		
AEs leading to discontinuation of carfilzomib	29	35		
AEs leading to discontinuation of dexamethasone	31	40		
Fatal adverse events	20	21		
Treatment-related adverse events (TRAEs)	176	180		
Treatment-related adverse events Grade ≥ 3	82	108		
Serious treatment-related adverse events	31	57		
TRAE leading to discontinuation of carfilzomib	11	23		
TRAEs leading to discontinuation of dexamethasone	13	29		
Fatal treatment-related adverse events	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Carfilzomib Concentration During Cycle 2

End point title	Plasma Carfilzomib Concentration During Cycle 2
End point description:	
Concentrations of carfilzomib in plasma were measured using a validated assay method. The lower limit of quantification was 0.100 ng/mL. "99999" indicates not applicable since participants in the twice weekly group received carfilzomib IV infusion for only 10 minutes.	
End point type	Secondary

End point timeframe:

Cycle 2 day 1 predose, 15 minutes after the start of infusion (once-weekly carfilzomib only), end of infusion, and 30 minutes after the end of infusion

End point values	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethason e	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethason e		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[9]	55		
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose	36.2 (± 162)	203 (± 1380)		
15 minutes after start of infusion*	99999 (± 99999)	1370 (± 1410)		
End of infusion	1640 (± 1900)	1130 (± 928)		
30 minutes after end of infusion	104 (± 293)	480 (± 2300)		

Notes:

[9] - *Participants in twice weekly Carfilzomib received IV for 10 minutes

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from the first dose of study drug up to 30 days after last dose; median (minimum, maximum) duration of treatment was 29.1 (0.1, 156.3) weeks and 38.0 (0.1, 158.3) weeks in each treatment group respectively.

Adverse event reporting additional description:

Deaths are reported from first dose of study drug until the end of study; median (minimum, maximum) follow-up time was 30.7 (0, 39) and 31.2 (0, 38) months in each treatment group respectively.

Three participants who died after randomization but before receiving any study treatment are not include in the table below.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone
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Reporting group description:

Participants received carfilzomib administered by IV infusion on days 1, 8, and 15 of each 28-day cycle (20 mg/m² on day 1 of cycle 1 and 70 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Reporting group title	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone
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Reporting group description:

Participants received carfilzomib administered by intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 of cycle 1 and 27 mg/m² thereafter). Participants also received 40 mg dexamethasone IV or orally on days 1, 8, 15 and 22 for the first 8 cycles; starting with cycle 9, dexamethasone was administered only on days 1, 8, and 15.

Serious adverse events	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	118 / 238 (49.58%)	102 / 235 (43.40%)	
number of deaths (all causes)	117	126	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	4 / 238 (1.68%)	7 / 235 (2.98%)	
occurrences causally related to treatment / all	0 / 4	1 / 7	
deaths causally related to treatment / all	0 / 4	1 / 7	
Plasmacytoma			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral neoplasm			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	4 / 235 (1.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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	2 / 238 (0.84%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site vesicles			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Critical illness			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Disease progression			
subjects affected / exposed	2 / 238 (0.84%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			

subjects affected / exposed	3 / 238 (1.26%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 238 (1.68%)	5 / 235 (2.13%)	
occurrences causally related to treatment / all	3 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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	2 / 238 (0.84%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
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 lung injury			

subjects affected / exposed	2 / 238 (0.84%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 238 (0.42%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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	6 / 238 (2.52%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 238 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Bradyphrenia			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 238 (0.42%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 238 (0.84%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	3 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoclonal immunoglobulin present			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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			
Contusion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 238 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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 myocardial infarction			
subjects affected / exposed	2 / 238 (0.84%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 238 (0.84%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 238 (1.26%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	3 / 238 (1.26%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 238 (0.42%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial mass			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (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	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 238 (1.68%)	8 / 235 (3.40%)	
occurrences causally related to treatment / all	0 / 4	3 / 13	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaemia folate deficiency			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia vitamin B12 deficiency			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			

subjects affected / exposed	3 / 238 (1.26%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 238 (0.84%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 238 (0.42%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
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 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haematoma			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	12 / 238 (5.04%)	8 / 235 (3.40%)	
occurrences causally related to treatment / all	4 / 15	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 238 (0.42%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	0 / 238 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 238 (0.84%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	3 / 238 (1.26%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 238 (0.42%)	4 / 235 (1.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	4 / 238 (1.68%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Influenza			
subjects affected / exposed	4 / 238 (1.68%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 238 (0.84%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
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 / 238 (1.26%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
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 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	23 / 238 (9.66%)	22 / 235 (9.36%)	
occurrences causally related to treatment / all	9 / 27	10 / 24	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pneumonia bacterial			

subjects affected / exposed	3 / 238 (1.26%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 238 (0.00%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 238 (1.26%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 238 (2.52%)	3 / 235 (1.28%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 2	
Septic shock			
subjects affected / exposed	5 / 238 (2.10%)	2 / 235 (0.85%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Spinal cord infection			

subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 238 (0.42%)	4 / 235 (1.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 238 (0.84%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection bacterial			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 238 (0.84%)	4 / 235 (1.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 235 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	4 / 238 (1.68%)	1 / 235 (0.43%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	

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

Non-serious adverse events	Once-weekly Carfilzomib 20/70 mg/m ² + Dexamethasone	Twice-weekly Carfilzomib 20/27 mg/m ² + Dexamethasone	
Total subjects affected by non-serious adverse events subjects affected / exposed	217 / 238 (91.18%)	204 / 235 (86.81%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	58 / 238 (24.37%) 85	49 / 235 (20.85%) 79	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	29 / 238 (12.18%) 44 50 / 238 (21.01%) 65 23 / 238 (9.66%) 29 55 / 238 (23.11%) 76 12 / 238 (5.04%) 17	29 / 235 (12.34%) 38 47 / 235 (20.00%) 66 26 / 235 (11.06%) 36 38 / 235 (16.17%) 55 4 / 235 (1.70%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	44 / 238 (18.49%) 73 27 / 238 (11.34%) 46	33 / 235 (14.04%) 50 21 / 235 (8.94%) 27	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	39 / 238 (16.39%) 47	49 / 235 (20.85%) 62	
Investigations			

Blood creatinine increased subjects affected / exposed occurrences (all)	14 / 238 (5.88%) 27	8 / 235 (3.40%) 9	
Neutrophil count decreased subjects affected / exposed occurrences (all)	12 / 238 (5.04%) 31	5 / 235 (2.13%) 18	
Platelet count decreased subjects affected / exposed occurrences (all)	27 / 238 (11.34%) 162	21 / 235 (8.94%) 59	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	28 / 238 (11.76%) 40	25 / 235 (10.64%) 33	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	69 / 238 (28.99%) 141	73 / 235 (31.06%) 168	
Neutropenia subjects affected / exposed occurrences (all)	20 / 238 (8.40%) 47	23 / 235 (9.79%) 50	
Thrombocytopenia subjects affected / exposed occurrences (all)	30 / 238 (12.61%) 78	19 / 235 (8.09%) 60	
Eye disorders Cataract subjects affected / exposed occurrences (all)	14 / 238 (5.88%) 18	13 / 235 (5.53%) 14	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	21 / 238 (8.82%) 25	22 / 235 (9.36%) 24	
Diarrhoea subjects affected / exposed occurrences (all)	53 / 238 (22.27%) 73	51 / 235 (21.70%) 75	
Nausea subjects affected / exposed occurrences (all)	38 / 238 (15.97%) 56	30 / 235 (12.77%) 38	

Vomiting subjects affected / exposed occurrences (all)	25 / 238 (10.50%) 46	17 / 235 (7.23%) 25	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	9 / 238 (3.78%) 9	13 / 235 (5.53%) 14	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	19 / 238 (7.98%) 24	15 / 235 (6.38%) 19	
Back pain subjects affected / exposed occurrences (all)	35 / 238 (14.71%) 45	31 / 235 (13.19%) 37	
Bone pain subjects affected / exposed occurrences (all)	20 / 238 (8.40%) 28	17 / 235 (7.23%) 21	
Muscle spasms subjects affected / exposed occurrences (all)	22 / 238 (9.24%) 30	20 / 235 (8.51%) 29	
Musculoskeletal pain subjects affected / exposed occurrences (all)	14 / 238 (5.88%) 16	12 / 235 (5.11%) 13	
Pain in extremity subjects affected / exposed occurrences (all)	17 / 238 (7.14%) 24	19 / 235 (8.09%) 22	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	31 / 238 (13.03%) 53	25 / 235 (10.64%) 35	
Respiratory tract infection subjects affected / exposed occurrences (all)	18 / 238 (7.56%) 37	23 / 235 (9.79%) 34	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	39 / 238 (16.39%) 59	28 / 235 (11.91%) 45	

Influenza			
subjects affected / exposed	13 / 238 (5.46%)	9 / 235 (3.83%)	
occurrences (all)	13	11	
Nasopharyngitis			
subjects affected / exposed	35 / 238 (14.71%)	30 / 235 (12.77%)	
occurrences (all)	61	50	
Pneumonia			
subjects affected / exposed	15 / 238 (6.30%)	5 / 235 (2.13%)	
occurrences (all)	18	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 238 (5.88%)	14 / 235 (5.96%)	
occurrences (all)	14	16	
Hypokalaemia			
subjects affected / exposed	20 / 238 (8.40%)	10 / 235 (4.26%)	
occurrences (all)	29	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2015	<ul style="list-style-type: none">- clarified that consent was required from subjects if additional blood samples were collected for pharmacokinetic (sparse sampling) and for the intensive pharmacokinetic/ pharmacodynamics substudy- clarified dexamethasone was to be administered orally on day 22 in cycles 1 to 9- clarified that dexamethasone was not to be administered on day 22 after cycle 9- clarified that events occurring before consent should have been captured as medical history information- clarified the timing of safety labs after cycle 4- clarified the timing of patient-reported outcome questionnaires
28 April 2015	<ul style="list-style-type: none">- added adverse events of pulmonary hypertension and TTP/HUS to the dose modification guidelines- clarified pharmacokinetic time points for intensive and sparse pharmacokinetic sampling.
22 April 2016	<ul style="list-style-type: none">- clarified timepoints for study procedures- clarified exclusion criteria of antineoplastic therapy use to allow immunotherapy or proteasome inhibitors- added the potential use of an IRC- removed information for formulation, physical description, storage, and investigational product accountability to avoid duplication with Investigational Product Instruction Manual- clarified carfilzomib and dexamethasone dosing and procedures for dose interruption- updated text to align with current carfilzomib core safety language- revised hematologic and nonhematologic toxicities for carfilzomib, and dexamethasone-related toxicities- clarified guidance for use of concomitant medications and therapies that were excluded- clarified that cytogenetic abnormalities from prior testing should have been reported as part of multiple myeloma history- added other radiologic modalities permitted for performing skeletal assessment (eg, low-dose CT scan)- clarified requirements for the discontinuation of subjects for PD- revised definition of adverse events regarding worsening of pre-existing conditions- clarified disease response for IMWG-URC
08 February 2017	<ul style="list-style-type: none">- changed PFS from a key secondary objective/endpoint to the primary objective/endpoint and ORR from the primary objective/endpoint to a key secondary objective/endpoint- revised the interim PFS analysis to monitor efficacy and allow the possibility of stopping the study early for efficacy; statistical language was aligned- updated stopping boundaries for PFS- updated carfilzomib dose modifications for nonhematologic toxicity- allowed for the possibility of long-term follow-up for overall survival- added sections for end of study, product complaints, and thromboprophylaxis- added sample forms for serious adverse event reporting and pregnancy and lactation notifications- updated background information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported