Clinical trial results:
A Randomized, Controlled, Phase 3 Study to Evaluate Optimized Retreatment and Prolonged Therapy With Bortezomib (VELCADE) in Patients With Multiple Myeloma in First or Second Relapse

Summary

EudraCT number	2011-004795-11
Trial protocol	IT BE SE FI PL NL DE PT
Global end of trial date	18 February 2016

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	26866138MMY3033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01910987
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.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	18 February 2016
Is this the analysis of the primary	No

completion data?	
Global end of trial reached?	Yes
Global end of trial date	18 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to describe the effect of optimized retreatment with bortezomib in combination with dexamethasone followed by prolonged therapy with bortezomib versus standard retreatment with bortezomib in combination with dexamethasone on progression free survival (PFS).

Protection of trial subjects:

Safety evaluations included monitoring of adverse events, clinical laboratory tests (hematology and serum chemistry), vital sign measurements, physical examinations, including neurological/peripheral neurological examinations and body weight measurement.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2013
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	Belgium: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Turkey: 23
Worldwide total number of subjects	80
EEA total number of subjects	55

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)	33
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 80 subjects (53 subjects- Group A and 27 subjects- Group B) were randomized in study and received study agent (intent-to-treat population and safety analysis set). Subjects who had progressive disease, discontinued bortezomib early or started an alternative multiple myeloma therapy were not eligible to enter in prolonged therapy period.

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?	No
Arm title	Group A

Arm description:

Subjects randomized to Group A started with 6 cycles of bortezomib 1.3 milligram per meter square (mg/m^2) subcutaneously (SC) and dexamethasone 20 milligram (mg) per oral (two 21-day cycles followed by four 35-day cycles; Optimized Retreatment) followed by a randomization, if criteria are met, into 1 of 2 prolonged therapy groups (A1 and A2).

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received bortezomib 1.3 mg/m^2 SC on Days 1, 4, 8, 11, every 21 days for Week 1-6 (Cycles 1 and 2) and on Days 1, 8, 15, 22, every 35 days for Week 7-26 (Cycles 3 to 6).

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

Dosage and administration details:

Subjects received dexamethasone 20 mg per oral (PO) on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-6 (Cycle 1 and 2) and on Days 1, 2, 8, 9, 15, 16, 22, 23, every 35 days for Week 7-26 (Cycle 3 to 6).

Arm title	Group A1 (Prolonged therapy)

Arm description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A1 and received bortezomib 1.3 mg/m^2 SC injection on Days 1, 8, 15, 22, every 35 days until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Arm type	Experimental

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received bortezomib 1.3 mg/m^2 SC injection on Days 1, 8, 15, 22, every 35 days.

Arm title	Group A2 (Prolonged therapy)

Arm description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A2 and received bortezomib 1.3 mg/m^2 SC once every other week, Days 1, 15, 29, 43, 57, 71, 85, and so on until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received bortezomib 1.3 mg/m^2 SC once every other week, Days 1, 15, 29, 43, 57, 71, 85, and so on until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Arm title	Group B (Standard retreatment)

Arm description:

Subjects randomly assigned to Group B received bortezomib 1.3 mg/m^2 SC injection on Days 1, 4, 8, 11, every 21 days and dexamethasone 20 mg tablet orally on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-24 (maximum of 8 cycles).

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received bortezomib 1.3 mg/m^2 SC injection on Days 1, 4, 8, 11, every 21 days for Week 1-24.

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

Dosage and administration details:

Subjects received dexamethasone 20 mg tablet orally on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-24.

Number of subjects in period 1	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)
Started	53	16	15
Completed	0	0	0
Not completed	53	16	15
Death	13	5	1
Other	7	1	3
Adverse event	1	-	-
Study end by sponsor	28	10	11
Consent withdrawn by subject	4	-	-

Number of subjects in period 1	Group B (Standard retreatment)		
Started	27		
Completed	0		
Not completed	27		
Death	8		
Other	1		
Adverse event	-		
Study end by sponsor	17		
Consent withdrawn by subject	1		

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Subjects randomized to Group A started with 6 cycles of bortezomib 1.3 milligram per meter square (mg/m^2) subcutaneously (SC) and dexamethasone 20 milligram (mg) per oral (two 21-day cycles followed by four 35-day cycles; Optimized Retreatment) followed by a randomization, if criteria are met, into 1 of 2 prolonged therapy groups (A1 and A2).	
Reporting group title	Group A1 (Prolonged therapy)
Reporting group description:	
Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A1 and received bortezomib 1.3 mg/m^2 SC injection on Days 1, 8, 15, 22, every 35 days until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).	
Reporting group title	Group A2 (Prolonged therapy)
Reporting group description:	
Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A2 and received bortezomib 1.3 mg/m^2 SC once every other week, Days 1, 15, 29, 43, 57, 71, 85, and so on until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).	
Reporting group title	Group B (Standard retreatment)
Reporting group description:	
Subjects randomly assigned to Group B received bortezomib 1.3 mg/m^2 SC injection on Days 1, 4, 8, 11, every 21 days and dexamethasone 20 mg tablet orally on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-24 (maximum of 8 cycles).	

Reporting group values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)
Number of subjects	53	16	15
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	8	5
From 65 to 84 years	33	8	10
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	66.6	65.5	68.6
standard deviation	± 8.88	± 8.94	± 8.58
Title for Gender Units: subjects			
Female	25	10	6
Male	28	6	9

Reporting group values	Group B (Standard retreatment)	Total	
Number of subjects	27	80	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	

Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	33	
From 65 to 84 years	14	47	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	64.3		
standard deviation	± 8.77	-	
Title for Gender Units: subjects			
Female	9	34	
Male	18	46	

End points

End points reporting groups

Reporting group title	Group A

Reporting group description:

Subjects randomized to Group A started with 6 cycles of bortezomib 1.3 milligram per meter square (mg/m^2) subcutaneously (SC) and dexamethasone 20 milligram (mg) per oral (two 21-day cycles followed by four 35-day cycles; Optimized Retreatment) followed by a randomization, if criteria are met, into 1 of 2 prolonged therapy groups (A1 and A2).

Reporting group title	Group A1 (Prolonged therapy)

Reporting group description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A1 and received bortezomib 1.3 mg/m^2 SC injection on Days 1, 8, 15, 22, every 35 days until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Reporting group title	Group A2 (Prolonged therapy)

Reporting group description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A2 and received bortezomib 1.3 mg/m^2 SC once every other week, Days 1, 15, 29, 43, 57, 71, 85, and so on until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Reporting group title	Group B (Standard retreatment)

Reporting group description:

Subjects randomly assigned to Group B received bortezomib 1.3 mg/m^2 SC injection on Days 1, 4, 8, 11, every 21 days and dexamethasone 20 mg tablet orally on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-24 (maximum of 8 cycles).

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[1]

End point description:

Progression free survival, defined as the time from randomization to time of diagnosis of disease progression or death due to any cause. The intent-to-treat (ITT) analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Primary

End point timeframe:

From randomization to time of disease progression or death, whichever occurs first (up to 2 years and 10 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not performed for this outcome measure.

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: months				
median (confidence interval 95%)	7.2 (5.7 to 9)	8.1 (6.7 to 10.8)	12 (7.5 to 21.4)	7.8 (4.9 to 11.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Response Rate (ORR)

End point title	Percentage of Subjects With Overall Response Rate (ORR)

End point description:

ORR defined as the best confirmed response including complete response (CR), very good partial response (VGPR) and partial response (PR). International Myeloma Working Group (IMWG) Criteria for progressive disease (PD): CR- Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and less than (<)5 percent (%) Plasma Cells (PCs) in bone marrow; VGPR- Serum and urine M-component detectable by immunofixation but not on electrophoresis or greater than or equal to (>=)90% reduction in serum M-component plus urine M-component <100 milligram (mg) per 24 hours and PR- >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200mg/24 hours. In addition, if present at baseline, >=50% reduction in the size of soft tissue plasmacytomas is also required. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

Up to end of treatment (30- 35 days after last dose of study drug)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: percentage of subjects				
number (not applicable)	66	93.8	80	51.9

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression, defined as the time from first randomization to time of diagnosis of disease progression. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received. Here 999 signifies "NE: Not Estimable" because upper limit of 95% CI was not estimable due to the lesser number of subjects who died during the study period.

End point type	Secondary

End point timeframe:

From randomization to disease progression or death, whichever occurs first (up to 2 years and 10 months)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: months				
median (confidence interval 95%)	7.4 (6.2 to 9)	8.1 (6.7 to 10.8)	12 (7.5 to 999)	7.8 (4.9 to 11.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response, defined as the time of first confirmed response (CR, VGPR, or PR) to time of diagnosis of disease progression. IMWG Criteria for PD: CR- Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and <5% PCs in bone marrow; VGPR- Serum and urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-component plus urine M-component <100mg per 24 hours and PR- >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200mg/24 hours. In addition, if present at baseline, >=50% reduction in the size of soft tissue plasmacytomas is also required. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment. Here 999 signifies "NE: Not Estimable" because upper limit of 95% CI was not estimable due to the lesser number of subjects who died during the study period.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented evidence of PD (up to 2 years and 10 months)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36[2]	15[3]	12[4]	13[5]
Units: months				
median (confidence interval 95%)	6.8 (5.6 to 10.4)	6.2 (5.6 to 7.9)	11.7 (6.8 to 999)	5.6 (2.3 to 8.8)

Notes:

[2] - Here 'N' signifies number of subjects analysed for this outcome measure.

[3] - Here 'N' signifies number of subjects analysed for this outcome measure.

[4] - Here 'N' signifies number of subjects analysed for this outcome measure.

[5] - Here 'N' signifies number of subjects analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Therapy (TTNT)

End point title	Time to Next Therapy (TTNT)

End point description:

Time to next therapy, defined as the time from first randomization to therapy to the start date of alternative multiple myeloma therapy. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

From first randomization to the start date of alternative multiple myeloma therapy (up to 2 years and 10 months)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: months				
median (confidence interval 95%)	8.6 (7.1 to 12.2)	12.4 (10.3 to 17.2)	13 (8.2 to 22.8)	9 (4.4 to 11.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival, defined as the time from first randomization to therapy to time of death due to any cause. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received. Here 999 represents "NE: Not Estimable" because median and upper limit of 95% CI was not estimable due to the lesser number of subjects who died during the study period.

End point type	Secondary

End point timeframe:

From first randomization to time of death due to any cause (up to 2 years and 10 months)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: months				
median (confidence interval 95%)	30.3 (25.2 to 30.3)	25.2 (22.5 to 999)	999 (21.4 to 999)	999 (19.1 to 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

The ECOG Performance Status was used to assess how a subjects's disease was progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis. The score ranges from 0 "fully active, able to carry on all pre-disease performance without restriction" to 5 "dead". The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, end of treatment (30- 35 days after last dose of study drug) and at endpoint (subjects last visit for efficacy evaluation)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: units on a scale				
arithmetic mean (standard deviation)				
At End of Treatment (n= 46, 14, 14, 26)	0.1 (± 0.74)	0 (± 0.78)	-0.1 (± 0.66)	0.3 (± 0.83)
At Endpoint (n= 52, 16, 15, 27)	0.1 (± 0.73)	-0.1 (± 0.77)	-0.1 (± 0.64)	0.3 (± 0.81)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions-5 Levels Questionnaire (EQ-5D-5L) Index Score

End point title	Change From Baseline in European Quality of Life-5 Dimensions-5 Levels Questionnaire (EQ-5D-5L) Index Score

End point description:

The EQ-5D-5L is a 5-item questionnaire instrument for use as a measure of health outcome. It has 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has 5 response levels (e.g., no problems with performing activity, slight problems, moderate problems, severe problems, unable to perform [extreme problems]). The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, end of treatment (30- 35 days after last dose of study drug) and at endpoint (subjects last visit for efficacy evaluation)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: units on a scale				
arithmetic mean (standard deviation)				
At End of Treatment (n= 23, 6, 6, 13)	-0.0485 (± 0.18659)	0.01 (± 0.1627)	0.0017 (± 0.19637)	-0.0625 (± 0.1433)
At Endpoint (n= 42, 12, 12, 26)	-0.0381 (± 0.18139)	-0.01 (± 0.16685)	-0.0363 (± 0.15088)	-0.0419 (± 0.18564)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality Visual Analogue Scale (EQ VAS)

End point title	Change From Baseline in European Quality Visual Analogue Scale (EQ VAS)

End point description:

EQ VAS is a “thermometer” visual analogue scale (VAS; referred to as EQ VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ VAS is used as a quantitative measure of health outcome as judged by the individual subject. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, end of treatment (30- 35 days after last dose of study drug) and at endpoint (subjects last visit for efficacy evaluation)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: units on a scale				
arithmetic mean (standard deviation)				
At End of Treatment (n= 23, 6, 6, 13)	2 (± 22.84)	4.5 (± 18.69)	22 (± 26.14)	-17.5 (± 25.55)
At Endpoint (n= 42, 12, 12, 26)	-2.5 (± 23.59)	7.2 (± 18.92)	4.3 (± 28.14)	-7.7 (± 24.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30)

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30)

End point description:

The EORTC QLQ-C30 incorporates 5 functional scales (physical, role, emotional, cognitive and social functioning), 1 global health and quality of life scale, 3 symptom scales (fatigue, nausea/vomiting and pain), and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). It is a 30-item questionnaire with responses ranging for the functional scales from not at all to very much and the global health/QOL ranging from very poor to excellent. Scores are transformed to 0-100 scale. The ITT analysis set was defined as all subjects randomly assigned to a treatment group, regardless of whether they received any treatment and the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline, at end of treatment (30-35 days after last dose of study drug) and at endpoint ((subjects last visit for efficacy evaluation)

End point values	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)	Group B (Standard retreatment)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	16	15	27
Units: units on a scale				
arithmetic mean (standard deviation)				
At End of Treatment (n= 23, 6, 6, 13)	2.5 (± 21.82)	-1.4 (± 15.29)	12.5 (± 25.69)	-13.5 (± 32.37)
At Endpoint (n= 42, 12, 12, 26)	1 (± 21.56)	4.2 (± 14.86)	6.9 (± 22.14)	-4.2 (± 31.56)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to end of study (maximum of 18 months after the last subject is enrolled in the study)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Group A

Reporting group description:

Subjects randomized to Group A started with 6 cycles of bortezomib 1.3 mg/m^2 SC and dexamethasone 20 mg per oral (two 21-day cycles
followed by four 35-day cycles; Optimized Retreatment) followed by a randomization, if criteria are met, into 1 of 2 prolonged therapy groups (A1 and A2).

Reporting group title	Group A1 (Prolonged therapy)

Reporting group description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A1 and received bortezomib 1.3 mg/m^2 SC injection on Days 1, 8, 15, 22, every 35 days until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Reporting group title	Group A2 (Prolonged therapy)

Reporting group description:

Subjects randomly assigned to Group A who completed the Optimized Retreatment period (6 cycles) and met the criteria for entry into Prolonged Therapy Period were randomised to Group A2 and received bortezomib 1.3 mg/m^2 SC once every other week, Days 1, 15, 29, 43, 57, 71, 85, and so on until disease progression, start of alternative MM therapy, or the end of the study (maximum of 18 months after the last subject was enrolled in the study).

Reporting group title	Group B (Standard retreatment)

Reporting group description:

Subjects randomly assigned to Group B received bortezomib 1.3 mg/m^2 SC injection on Days 1, 4, 8, 11, every 21 days and dexamethasone 20 mg tablet orally on Days 1, 2, 4, 5, 8, 9, 11, 12, every 21 days for Week 1-24 (maximum of 8 cycles).

Serious adverse events	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 53 (33.96%)	5 / 16 (31.25%)	3 / 15 (20.00%)
number of deaths (all causes)	5	1	0
number of deaths resulting from adverse events			
Vascular disorders			
Embolism Venous			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma Cell Leukaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	3 / 53 (5.66%)	2 / 16 (12.50%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cognitive Disorder			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multi-Organ Failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Distension			

subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestinal Obstruction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypercalcaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 53 (5.66%)	2 / 16 (12.50%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary Tract Infection			

subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group B (Standard retreatment)		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Vascular disorders			
Embolism Venous			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma Cell Leukaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cognitive Disorder			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-Organ Failure			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric Haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large Intestinal Obstruction			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group A	Group A1 (Prolonged therapy)	Group A2 (Prolonged therapy)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 53 (96.23%)	16 / 16 (100.00%)	15 / 15 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 53 (7.55%)	2 / 16 (12.50%)	0 / 15 (0.00%)
occurrences (all)	4	2	0
Hypotension			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	3 / 15 (20.00%)
occurrences (all)	5	0	3
Pallor			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Peripheral Artery Aneurysm			

subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 53 (13.21%)	3 / 16 (18.75%)	3 / 15 (20.00%)
occurrences (all)	11	5	4
Chest Pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Chills			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	9 / 53 (16.98%)	3 / 16 (18.75%)	1 / 15 (6.67%)
occurrences (all)	9	3	1
Face Oedema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Influenza Like Illness			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Injection Site Erythema			
subjects affected / exposed	2 / 53 (3.77%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Injection Site Pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Injection Site Reaction			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Injection Site Rash			

subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	15	15	0
Injection Site Vasculitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	12 / 53 (22.64%)	3 / 16 (18.75%)	3 / 15 (20.00%)
occurrences (all)	19	9	3
Oedema Peripheral			
subjects affected / exposed	8 / 53 (15.09%)	2 / 16 (12.50%)	2 / 15 (13.33%)
occurrences (all)	9	2	3
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	3 / 53 (5.66%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Hallucination, Visual			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	9 / 53 (16.98%)	2 / 16 (12.50%)	5 / 15 (33.33%)
occurrences (all)	16	2	6
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Erectile Dysfunction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Spinal Compression Fracture			

subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Blood Testosterone Decreased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Light Chain Analysis Increased			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	3 / 53 (5.66%)	2 / 16 (12.50%)	0 / 15 (0.00%)
occurrences (all)	5	4	0
Angina Pectoris			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Cardiac Failure			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Cardiomyopathy			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Mitral Valve Incompetence			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Sinus Tachycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	9 / 53 (16.98%)	3 / 16 (18.75%)	3 / 15 (20.00%)
occurrences (all)	10	3	4
Cough			
subjects affected / exposed	10 / 53 (18.87%)	2 / 16 (12.50%)	2 / 15 (13.33%)
occurrences (all)	13	3	2
Dyspnoea Exertional			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Productive Cough			
subjects affected / exposed	3 / 53 (5.66%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Pulmonary Oedema			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 53 (20.75%)	2 / 16 (12.50%)	2 / 15 (13.33%)
occurrences (all)	16	4	2
Neutropenia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	11	2	0
Leukocytosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Neutrophilia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Thrombocytopenia			
subjects affected / exposed	7 / 53 (13.21%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	24	4	8
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Amnesia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)

occurrences (all)	1	1	0
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dizziness			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dizziness Postural			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dysaesthesia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	4 / 53 (7.55%)	1 / 16 (6.25%)	2 / 15 (13.33%)
occurrences (all)	6	2	3
Hypersomnia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Hypertonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Neuralgia			
subjects affected / exposed	3 / 53 (5.66%)	2 / 16 (12.50%)	1 / 15 (6.67%)
occurrences (all)	3	2	1
Neuropathy Peripheral			
subjects affected / exposed	4 / 53 (7.55%)	3 / 16 (18.75%)	0 / 15 (0.00%)
occurrences (all)	9	8	0
Paraesthesia			
subjects affected / exposed	7 / 53 (13.21%)	3 / 16 (18.75%)	1 / 15 (6.67%)
occurrences (all)	7	3	1
Sciatica			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)

occurrences (all)	1	0	1
Peripheral Sensory Neuropathy			
subjects affected / exposed	8 / 53 (15.09%)	3 / 16 (18.75%)	4 / 15 (26.67%)
occurrences (all)	17	3	13
Tremor			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dry Eye			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	3	0	3
Eye Disorder			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Glaucoma			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Panophthalmitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pterygium			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Visual Acuity Reduced			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 53 (3.77%)	2 / 16 (12.50%)	0 / 15 (0.00%)
occurrences (all)	2	2	0

Abdominal Pain Upper			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	3 / 15 (20.00%)
occurrences (all)	4	0	3
Constipation			
subjects affected / exposed	13 / 53 (24.53%)	3 / 16 (18.75%)	5 / 15 (33.33%)
occurrences (all)	16	4	6
Diarrhoea			
subjects affected / exposed	10 / 53 (18.87%)	3 / 16 (18.75%)	4 / 15 (26.67%)
occurrences (all)	15	3	9
Dyspepsia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Tongue Ulceration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	3 / 53 (5.66%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Vomiting			
subjects affected / exposed	4 / 53 (7.55%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	4	1	1
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	5 / 53 (9.43%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	6	0	2
Hyperhidrosis			
subjects affected / exposed	3 / 53 (5.66%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Nail Dystrophy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	3 / 53 (5.66%)	0 / 16 (0.00%)	2 / 15 (13.33%)

occurrences (all)	3	0	2
Rash			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	5	0	3
Rash Erythematous			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Skin Mass			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Skin Lesion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Skin Ulcer			
subjects affected / exposed	2 / 53 (3.77%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Swelling Face			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Back Pain			
subjects affected / exposed	6 / 53 (11.32%)	0 / 16 (0.00%)	6 / 15 (40.00%)
occurrences (all)	6	0	6
Bone Pain			
subjects affected / exposed	6 / 53 (11.32%)	3 / 16 (18.75%)	1 / 15 (6.67%)
occurrences (all)	9	5	1
Muscle Spasms			
subjects affected / exposed	6 / 53 (11.32%)	2 / 16 (12.50%)	2 / 15 (13.33%)
occurrences (all)	6	2	2
Musculoskeletal Chest Pain			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	6	0	2

Musculoskeletal Pain			
subjects affected / exposed	3 / 53 (5.66%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	3	0	2
Myalgia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	3	0	2
Musculoskeletal Stiffness			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Osteolysis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pain in Extremity			
subjects affected / exposed	6 / 53 (11.32%)	0 / 16 (0.00%)	3 / 15 (20.00%)
occurrences (all)	9	0	6
Pain in Jaw			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	3	0	1
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Decreased Appetite			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	6	0	2
Hyperglycaemia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	5	1	2
Hypocalcaemia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Hyperkalaemia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 16 (0.00%)	1 / 15 (6.67%)

occurrences (all)	3	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 53 (9.43%)	3 / 16 (18.75%)	1 / 15 (6.67%)
occurrences (all)	6	4	1
Conjunctivitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Herpes Virus Infection			
subjects affected / exposed	2 / 53 (3.77%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Hordeolum			
subjects affected / exposed	2 / 53 (3.77%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	4 / 53 (7.55%)	0 / 16 (0.00%)	3 / 15 (20.00%)
occurrences (all)	4	0	3
Localised Infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	2
Nasopharyngitis			
subjects affected / exposed	4 / 53 (7.55%)	1 / 16 (6.25%)	1 / 15 (6.67%)
occurrences (all)	5	1	1
Oral Infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pneumonia			

subjects affected / exposed	5 / 53 (9.43%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	6	1	0
Respiratory Tract Infection			
subjects affected / exposed	4 / 53 (7.55%)	3 / 16 (18.75%)	1 / 15 (6.67%)
occurrences (all)	7	6	1
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 53 (11.32%)	1 / 16 (6.25%)	3 / 15 (20.00%)
occurrences (all)	7	1	4
Urinary Tract Infection			
subjects affected / exposed	1 / 53 (1.89%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Group B (Standard retreatment)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	8		
Pallor			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Peripheral Artery Aneurysm			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasmacytoma			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	11		

Chest Pain				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Chills				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	4			
Fatigue				
subjects affected / exposed	7 / 27 (25.93%)			
occurrences (all)	10			
Face Oedema				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Influenza Like Illness				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Injection Site Erythema				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			
Injection Site Pain				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Injection Site Reaction				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Injection Site Rash				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Injection Site Vasculitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Pyrexia				
subjects affected / exposed	4 / 27 (14.81%)			
occurrences (all)	5			
Oedema Peripheral				
subjects affected / exposed	5 / 27 (18.52%)			
occurrences (all)	5			

Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hallucination, Visual			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Erectile Dysfunction			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Spinal Compression Fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Blood Testosterone Decreased			
subjects affected / exposed	0 / 27 (0.00%)		

occurrences (all)	0		
Light Chain Analysis Increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Angina Pectoris			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Cardiac Failure			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Cardiomyopathy			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Mitral Valve Incompetence			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Sinus Tachycardia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	8		
Dyspnoea Exertional			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Productive Cough			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

Pulmonary Oedema subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 9		
Neutropenia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4		
Leukocytosis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Neutrophilia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 10		
Nervous system disorders Ageusia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Amnesia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Carpal Tunnel Syndrome subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4		
Dizziness Postural subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Dysgeusia			

subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Dysaesthesia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hypersomnia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hypertonia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Neuropathy Peripheral			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	14		
Paraesthesia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Peripheral Sensory Neuropathy			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Eye disorders			

Cataract			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dry Eye			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Eye Disorder			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Glaucoma			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Panophthalmitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Pterygium			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Visual Acuity Reduced			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Abdominal Pain Upper			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	17		
Dyspepsia			
subjects affected / exposed	1 / 27 (3.70%)		

occurrences (all)	1		
Tongue Ulceration			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	8		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Nail Dystrophy			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	6		
Rash Erythematous			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Skin Mass			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

Skin Lesion			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Skin Ulcer			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Swelling Face			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Back Pain			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Bone Pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Muscle Spasms			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Musculoskeletal Pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Osteolysis			
subjects affected / exposed	2 / 27 (7.41%)		

occurrences (all)	2		
Pain in Extremity			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Pain in Jaw			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Decreased Appetite			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

Conjunctivitis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	2			
Herpes Virus Infection				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	2			
Localised Infection				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Oral Infection				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	0 / 27 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	2			
Respiratory Tract Infection				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences (all)	4			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Urinary Tract Infection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2012	The first amendment included the following changes: 1) Bortezomib dose and schedule in the control group (Group B) was updated to reflect the bortezomib schedule given in the Summary of Product Characteristics (SmPC), 2) change in study design and description of study phases and periods based on addition of 2 randomizations, with the first one performed at inclusion (pretreatment on Day 1 of Cycle 1) to randomly assign subjects to an "optimized" retreatment group (Group A), which could potentially reduce the drop-out rate and increase protocol adherence, or to a control group (Group B) that received standard retreatment. A second randomization performed at the end of the optimized retreatment period (Group A only) that was included to describe 2 schedules of prolonged therapy following the initial optimized retreatment period, 3) eligibility criteria for entry into optimized prolonged therapy (Group A) revised, 4) primary, secondary, and exploratory objectives, hypothesis, endpoints, sample size, and statistical methods were updated to reflect the new study design, 5) end of the study was changed to event-driven (disease progression or death) and 6) adverse event reporting and use of information and publication standard text updated.
01 August 2014	The second amendment incorporated the rationale and details for the premature closure of enrollment, clarification of collection period for survival data, removal of formal statistical testing, inclusion of descriptive statistical analyses for efficacy endpoints, and some minor editorial changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to a reduced commitment towards enrollment of subjects, the sponsor decided to stop the study early. Consequently, low number of subjects and inadequate statistical power were study limitations.

Notes:

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