Clinical trial results:
A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF POMALIDOMIDE, BORTEZOMIB AND LOW-DOSE DEXAMETHASONE VERSUS BORTEZOMIB AND LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Summary

EudraCT number	2014-000268-17
Trial protocol	IE NO DK SE FI ES PT AT PL GR FR IT
Global end of trial date	13 May 2022

Results information

Result version number	v1 (current)
This version publication date	25 May 2023
First version publication date	25 May 2023

Trial information

Trial identification

Sponsor protocol code	CC-4047-MM-007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of POM + BTZ + LD-DEX with BTZ + LD-DEX in subjects with relapsed or refractory MM

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2016
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	Austria: 8
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 33
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 69
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Turkey: 55
Country: Number of subjects enrolled	United Kingdom: 58

Country: Number of subjects enrolled	United States: 122
Worldwide total number of subjects	559
EEA total number of subjects	280

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)	229
From 65 to 84 years	323
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

548 participants treated

Period 1

Period 1 title	Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment 1: POM+BTZ+LD-DEX

Arm description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravascular use , Subcutaneous use

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle
The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

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

Dosage and administration details:

For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.
For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Investigational medicinal product name	pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 mg, 2 mg, 3 mg, and 4 mg

Arm title	Treatment 2: BTZ+LD-DEX

Arm description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

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

Dosage and administration details:

For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.
For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravascular use , Subcutaneous use

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle
The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

Number of subjects in period 1	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX
Started	281	278
Completed	278	270
Not completed	3	8
Physician decision	-	1
Consent withdrawn by subject	-	4
death	1	-
Progressive Disease	-	2
Lost to follow-up	1	-
Randomization Error	1	-
clinical progression	-	1

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment 1: POM+BTZ+LD-DEX

Arm description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravascular use , Subcutaneous use

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle
The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

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

Dosage and administration details:

2 mg and 4 mg

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 mg, 2 mg, 3 mg, and 4 mg

Arm title	Treatment 2: BTZ+LD-DEX

Arm description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

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

Dosage and administration details: 2 mg and 4 mg	
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravascular use , Subcutaneous use

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle
The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

Number of subjects in period 2	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX
Started	278	270
Completed	0	0
Not completed	278	270
Withdrawal of Consent	25	22
Adverse event, serious fatal	20	9
Adverse event, non-fatal	39	52
Other Reasons	27	19
Progressive Disease	167	165
Pregnancy	-	1
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment 1: POM+BTZ+LD-DEX
Reporting group description:	
POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.	
Reporting group title	Treatment 2: BTZ+LD-DEX
Reporting group description:	
BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.	

Reporting group values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX	Total
Number of subjects	281	278	559
Age categorical Units: Subjects			
Adults (18-64 years)	114	115	229
From 65-84 years	164	159	323
85 years and over	3	4	7
Age Continuous Units: Years			
arithmetic mean	65.9	66.1	
standard deviation	± 10.13	± 10.16	-
Sex: Female, Male Units: Participants			
Female	126	131	257
Male	155	147	302
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	14	8	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	13	21
White	237	234	471
More than one race	0	0	0
Unknown or Not Reported	22	23	45
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	17	14	31
Not Hispanic or Latino	244	241	485
Unknown or Not Reported	20	23	43

End points

End points reporting groups

Reporting group title	Treatment 1: POM+BTZ+LD-DEX

Reporting group description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Reporting group title	Treatment 2: BTZ+LD-DEX

Reporting group description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Reporting group title	Treatment 1: POM+BTZ+LD-DEX

Reporting group description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Reporting group title	Treatment 2: BTZ+LD-DEX

Reporting group description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Primary: Progression Free Survival by Independent Response Adjudication Committee (IRAC)

End point title	Progression Free Survival by Independent Response Adjudication Committee (IRAC)

End point description:

Progression free survival (PFS) will be calculated as the time between the randomization and progressive disease (PD) or death.

Progressive Disease is defined as an Increase of ≥ 25% from nadir in:
-Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)g
-Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours)
-In patients without measurable serum and urine M-protein levels the difference between involved and uninvolved FLC levels, the absolute increase must be > 100 mg/dL.
-Bone marrow plasma cell percentage, the absolute % must be ≥ 10%h
-Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas. -Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

End point type	Primary

End point timeframe:

From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	278		
Units: Months				
median (confidence interval 95%)	11.20 (9.66 to 13.73)	7.10 (5.88 to 8.48)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.77

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) is calculated as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

From randomization to date of death, up to approximately 65 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	278		
Units: Months				
median (confidence interval 95%)	35.58 (28.55 to 41.20)	31.61 (26.05 to 37.16)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
Comparison groups	Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.571
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.15

Secondary: Overall Response Rate by Independent Response Adjudication Committee (IRAC)

End point title	Overall Response Rate by Independent Response Adjudication Committee (IRAC)

End point description:

The ORR together with the relative proportions in each response category (ie, stringent CR [sCR], CR, very good PR [VGPR], PR, SD, and PD) by treatment using the IMWG criteria will be examined.

Complete Response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow

SCR: CR+ Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine Mprotein level < 100 mg per 24 hours

PR: ≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours

Progressive Disease: Please refer to Primary outcome measure for definition

SD: Not meeting criteria for CR, VGPR, PR, or progressive disease

End point type	Secondary

End point timeframe:

From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	278		
Units: Participants				
Stringent Complete Response	9	2		
Complete Response	35	9		
Very Good Partial Response	104	40		
Partial Response	83	88		
Stable Disease	32	106		
Progressive Disease	11	16		
Not Evaluable	7	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response by Independent Response Adjudication Committee (IRAC)

End point title	Duration of Response by Independent Response Adjudication Committee (IRAC)

End point description:

Duration of myeloma response is defined as the duration from the time when the IMWG response criteria are first met for sCR or CR or VGPR or PR until the first date the response criteria are met for PD or until the subject died from any cause, whichever occurs first.

Complete Response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow

SCR: CR+ Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine Mprotein level < 100 mg per 24 hours

PR: ≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours

Progressive Disease: Please refer to Primary outcome measure for definition

SD: Not meeting criteria for CR, VGPR, PR, or progressive disease

End point type	Secondary

End point timeframe:

From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	139		
Units: Months				
median (confidence interval 95%)	13.70 (10.94 to 18.10)	10.94 (8.11 to 14.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DOR
Comparison groups	Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.064
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.02

Secondary: Number of Participants with grade 3-4 Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with grade 3-4 Treatment Emergent Adverse Events (TEAE)

End point description:

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose date of the study treatment and within 28 days after the last dose date.

End point type	Secondary

End point timeframe:

From first dose to 28 days after the last dose (up to approximately 44 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	270		
Units: Participants	259	194		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with grade 5 Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with grade 5 Treatment Emergent Adverse Events (TEAE)

End point description:

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose date of the study treatment and within 28 days after the last dose date.

End point type	Secondary

End point timeframe:

From first dose to 28 days after the last dose (up to approximately 44 months

End point values	Treatment 1: POM+BTZ+LD-DEX	Treatment 2: BTZ+LD-DEX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	270		
Units: Participants	29	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs: From first treatment to 28 days after last dose, up to approximately 44 months on average of 10 months.

All-Cause mortality: from randomization to end of the study, approximately 65 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	BTZ + LD-DEX

Reporting group description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Reporting group title	POM + BTZ + LD-DEX

Reporting group description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Serious adverse events	BTZ + LD-DEX	POM + BTZ + LD-DEX	
Total subjects affected by serious adverse events			
subjects affected / exposed	119 / 270 (44.07%)	177 / 278 (63.67%)	
number of deaths (all causes)	190	196	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 270 (0.37%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 1	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasmacytoma			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Porocarcinoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal cancer			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 270 (0.74%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	4 / 270 (1.48%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	1 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 270 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (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			
General physical health deterioration			
subjects affected / exposed	9 / 270 (3.33%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 4	
Death			
subjects affected / exposed	0 / 270 (0.00%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	2 / 4	
Fatigue			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	2 / 270 (0.74%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza like illness			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 270 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 270 (1.85%)	12 / 278 (4.32%)	
occurrences causally related to treatment / all	2 / 5	7 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 270 (0.74%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory acidosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute pulmonary oedema			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 270 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 270 (0.37%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	3 / 270 (1.11%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 270 (0.37%)	9 / 278 (3.24%)	
occurrences causally related to treatment / all	0 / 1	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory alkalosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 270 (0.74%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Coronavirus test positive			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest X-ray abnormal			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 270 (1.11%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 270 (0.74%)	9 / 278 (3.24%)	
occurrences causally related to treatment / all	0 / 2	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Cardiac failure congestive			
subjects affected / exposed	2 / 270 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 270 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 270 (0.74%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	5 / 270 (1.85%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 5	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 270 (0.37%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 270 (1.85%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	1 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperviscosity syndrome			
subjects affected / exposed	3 / 270 (1.11%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	3 / 270 (1.11%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 270 (0.74%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 270 (2.22%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	6 / 9	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric volvulus			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 270 (1.11%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
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	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 270 (1.11%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	6 / 270 (2.22%)	8 / 278 (2.88%)	
occurrences causally related to treatment / all	0 / 7	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anuria			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical spinal stenosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteorrhagia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 270 (0.74%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	1 / 270 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 270 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis pneumococcal			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 270 (0.00%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (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	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	4 / 270 (1.48%)	10 / 278 (3.60%)	
occurrences causally related to treatment / all	0 / 4	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterococcal sepsis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 270 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemophilus infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes oesophagitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hordeolum			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 270 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterobacter pneumonia			

subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leishmaniasis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	5 / 270 (1.85%)	10 / 278 (3.60%)	
occurrences causally related to treatment / all	3 / 6	2 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	2 / 270 (0.74%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis listeria			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
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 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			

subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (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 bacterial			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia moraxella			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 270 (0.74%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia streptococcal			
subjects affected / exposed	2 / 270 (0.74%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	17 / 270 (6.30%)	34 / 278 (12.23%)	
occurrences causally related to treatment / all	15 / 23	19 / 45	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 270 (0.37%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 270 (0.00%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 270 (0.37%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 270 (0.00%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinusitis			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal sepsis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
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	3 / 270 (1.11%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 270 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 270 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 270 (0.74%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 270 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 270 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 270 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (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	0 / 270 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 270 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BTZ + LD-DEX	POM + BTZ + LD-DEX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	260 / 270 (96.30%)	276 / 278 (99.28%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 270 (4.81%)	26 / 278 (9.35%)	
occurrences (all)	16	34	
Hypertension			
subjects affected / exposed	22 / 270 (8.15%)	24 / 278 (8.63%)	
occurrences (all)	26	32	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	33 / 270 (12.22%)	72 / 278 (25.90%)	
occurrences (all)	43	110	
Oedema peripheral			
subjects affected / exposed	54 / 270 (20.00%)	101 / 278 (36.33%)	
occurrences (all)	60	124	
Influenza like illness			
subjects affected / exposed	9 / 270 (3.33%)	15 / 278 (5.40%)	
occurrences (all)	19	23	
Fatigue			

subjects affected / exposed	72 / 270 (26.67%)	107 / 278 (38.49%)	
occurrences (all)	84	129	
Asthenia			
subjects affected / exposed	48 / 270 (17.78%)	52 / 278 (18.71%)	
occurrences (all)	65	85	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 270 (16.67%)	66 / 278 (23.74%)	
occurrences (all)	64	101	
Dyspnoea			
subjects affected / exposed	32 / 270 (11.85%)	62 / 278 (22.30%)	
occurrences (all)	35	85	
Oropharyngeal pain			
subjects affected / exposed	16 / 270 (5.93%)	17 / 278 (6.12%)	
occurrences (all)	21	18	
Productive cough			
subjects affected / exposed	13 / 270 (4.81%)	17 / 278 (6.12%)	
occurrences (all)	17	21	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	17 / 270 (6.30%)	13 / 278 (4.68%)	
occurrences (all)	19	15	
Depression			
subjects affected / exposed	7 / 270 (2.59%)	16 / 278 (5.76%)	
occurrences (all)	7	16	
Insomnia			
subjects affected / exposed	54 / 270 (20.00%)	49 / 278 (17.63%)	
occurrences (all)	61	61	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 270 (1.11%)	14 / 278 (5.04%)	
occurrences (all)	3	21	
Weight decreased			
subjects affected / exposed	18 / 270 (6.67%)	20 / 278 (7.19%)	
occurrences (all)	18	21	
Weight increased			

subjects affected / exposed	19 / 270 (7.04%)	19 / 278 (6.83%)	
occurrences (all)	22	26	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	11 / 270 (4.07%)	35 / 278 (12.59%)	
occurrences (all)	20	71	
Fall			
subjects affected / exposed	11 / 270 (4.07%)	20 / 278 (7.19%)	
occurrences (all)	19	38	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 270 (1.85%)	26 / 278 (9.35%)	
occurrences (all)	5	31	
Nervous system disorders			
Dizziness			
subjects affected / exposed	29 / 270 (10.74%)	49 / 278 (17.63%)	
occurrences (all)	36	66	
Dysgeusia			
subjects affected / exposed	8 / 270 (2.96%)	18 / 278 (6.47%)	
occurrences (all)	8	19	
Headache			
subjects affected / exposed	25 / 270 (9.26%)	35 / 278 (12.59%)	
occurrences (all)	36	52	
Hypoaesthesia			
subjects affected / exposed	15 / 270 (5.56%)	7 / 278 (2.52%)	
occurrences (all)	15	7	
Paraesthesia			
subjects affected / exposed	5 / 270 (1.85%)	18 / 278 (6.47%)	
occurrences (all)	5	22	
Peripheral sensory neuropathy			
subjects affected / exposed	103 / 270 (38.15%)	133 / 278 (47.84%)	
occurrences (all)	133	197	
Syncope			
subjects affected / exposed	6 / 270 (2.22%)	14 / 278 (5.04%)	
occurrences (all)	7	16	
Tremor			

subjects affected / exposed	8 / 270 (2.96%)	32 / 278 (11.51%)	
occurrences (all)	9	36	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	12 / 270 (4.44%)	18 / 278 (6.47%)	
occurrences (all)	13	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	72 / 270 (26.67%)	87 / 278 (31.29%)	
occurrences (all)	111	142	
Leukopenia			
subjects affected / exposed	9 / 270 (3.33%)	37 / 278 (13.31%)	
occurrences (all)	10	87	
Thrombocytopenia			
subjects affected / exposed	105 / 270 (38.89%)	110 / 278 (39.57%)	
occurrences (all)	178	196	
Neutropenia			
subjects affected / exposed	29 / 270 (10.74%)	150 / 278 (53.96%)	
occurrences (all)	45	575	
Lymphopenia			
subjects affected / exposed	9 / 270 (3.33%)	14 / 278 (5.04%)	
occurrences (all)	34	41	
Eye disorders			
Vision blurred			
subjects affected / exposed	9 / 270 (3.33%)	14 / 278 (5.04%)	
occurrences (all)	9	14	
Cataract			
subjects affected / exposed	3 / 270 (1.11%)	22 / 278 (7.91%)	
occurrences (all)	3	26	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	25 / 270 (9.26%)	22 / 278 (7.91%)	
occurrences (all)	25	24	
Dry mouth			
subjects affected / exposed	11 / 270 (4.07%)	19 / 278 (6.83%)	
occurrences (all)	11	21	
Diarrhoea			

subjects affected / exposed	82 / 270 (30.37%)	102 / 278 (36.69%)	
occurrences (all)	137	202	
Constipation			
subjects affected / exposed	65 / 270 (24.07%)	106 / 278 (38.13%)	
occurrences (all)	81	158	
Abdominal pain upper			
subjects affected / exposed	16 / 270 (5.93%)	23 / 278 (8.27%)	
occurrences (all)	18	28	
Abdominal pain			
subjects affected / exposed	19 / 270 (7.04%)	30 / 278 (10.79%)	
occurrences (all)	20	41	
Abdominal distension			
subjects affected / exposed	6 / 270 (2.22%)	17 / 278 (6.12%)	
occurrences (all)	6	19	
Nausea			
subjects affected / exposed	56 / 270 (20.74%)	52 / 278 (18.71%)	
occurrences (all)	67	75	
Vomiting			
subjects affected / exposed	27 / 270 (10.00%)	35 / 278 (12.59%)	
occurrences (all)	41	49	
Stomatitis			
subjects affected / exposed	1 / 270 (0.37%)	17 / 278 (6.12%)	
occurrences (all)	1	20	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	11 / 270 (4.07%)	31 / 278 (11.15%)	
occurrences (all)	11	36	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 270 (11.85%)	39 / 278 (14.03%)	
occurrences (all)	36	52	
Back pain			
subjects affected / exposed	38 / 270 (14.07%)	61 / 278 (21.94%)	
occurrences (all)	41	84	
Bone pain			

subjects affected / exposed	14 / 270 (5.19%)	25 / 278 (8.99%)	
occurrences (all)	15	33	
Muscle spasms			
subjects affected / exposed	16 / 270 (5.93%)	30 / 278 (10.79%)	
occurrences (all)	17	39	
Muscular weakness			
subjects affected / exposed	12 / 270 (4.44%)	41 / 278 (14.75%)	
occurrences (all)	14	44	
Musculoskeletal pain			
subjects affected / exposed	17 / 270 (6.30%)	23 / 278 (8.27%)	
occurrences (all)	21	24	
Myalgia			
subjects affected / exposed	11 / 270 (4.07%)	15 / 278 (5.40%)	
occurrences (all)	12	16	
Pain in extremity			
subjects affected / exposed	38 / 270 (14.07%)	42 / 278 (15.11%)	
occurrences (all)	44	47	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	18 / 270 (6.67%)	36 / 278 (12.95%)	
occurrences (all)	21	80	
Urinary tract infection			
subjects affected / exposed	28 / 270 (10.37%)	36 / 278 (12.95%)	
occurrences (all)	42	76	
Upper respiratory tract infection			
subjects affected / exposed	51 / 270 (18.89%)	71 / 278 (25.54%)	
occurrences (all)	79	156	
Respiratory tract infection			
subjects affected / exposed	16 / 270 (5.93%)	21 / 278 (7.55%)	
occurrences (all)	17	33	
Pneumonia			
subjects affected / exposed	21 / 270 (7.78%)	26 / 278 (9.35%)	
occurrences (all)	26	30	
Lower respiratory tract infection			
subjects affected / exposed	8 / 270 (2.96%)	17 / 278 (6.12%)	
occurrences (all)	9	40	

Influenza			
subjects affected / exposed	13 / 270 (4.81%)	27 / 278 (9.71%)	
occurrences (all)	14	44	
Conjunctivitis			
subjects affected / exposed	16 / 270 (5.93%)	26 / 278 (9.35%)	
occurrences (all)	19	36	
Bronchitis			
subjects affected / exposed	20 / 270 (7.41%)	43 / 278 (15.47%)	
occurrences (all)	30	66	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 270 (9.63%)	29 / 278 (10.43%)	
occurrences (all)	28	31	
Hyperglycaemia			
subjects affected / exposed	28 / 270 (10.37%)	43 / 278 (15.47%)	
occurrences (all)	48	82	
Hypocalcaemia			
subjects affected / exposed	10 / 270 (3.70%)	20 / 278 (7.19%)	
occurrences (all)	11	42	
Hypokalaemia			
subjects affected / exposed	31 / 270 (11.48%)	45 / 278 (16.19%)	
occurrences (all)	51	81	
Hypomagnesaemia			
subjects affected / exposed	7 / 270 (2.59%)	20 / 278 (7.19%)	
occurrences (all)	9	23	
Hypophosphataemia			
subjects affected / exposed	10 / 270 (3.70%)	20 / 278 (7.19%)	
occurrences (all)	21	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	-Updated route of administration for the bortezomib in both treatment arms to subcutaneous from intravenous-Added quality of life assessment to allow an exploratory evaluation of the differences in health-related quality of life- Added biomarker sampling to allow for an exploratory evaluation of Minimal Residue Disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures-Added an endpoint to allow for an exploratory evaluation of the Progression-free survival after next-line therapy (PFS2)
14 November 2014	The main purpose of this protocol amendment is to allow for the expansion of trial enrollment to countries and sites outside of the US in order to aid in completing enrollment. The changes outlined throughout this document are required in order to expand globally; including updates to the Investigational Product sections and the collection of both Exploratory Biomarker samples and Quality of Life information.
16 October 2015	Approval status of Pomalyst in the United States has been updated following full approval notification on 23 April 2015 Reduction in overall sample sizeUpdates to time points for contraceptive requirements and pregnancy testing
09 December 2015	Revision in overall sample size Updated Sections: Protocol Summary, Section 4.1, Section 7.1, Section 10.3, Section 10.9, Section 10.10
14 June 2017	Perform the final PFS analysis before the originally planned PFS events (381) are reached -Updated statistical considerations for the study will be specified in the protocol amendment and revised statistical analysis plan (SAP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported