Clinical trial results:
A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral Ixazomib (MLN9708) Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Summary

EudraCT number	2011-005496-17
Trial protocol	DE BE GB HU PT AT ES CZ SE IT FR NL DK PL
Global end of trial date	07 February 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

Trial information

Trial identification

Sponsor protocol code	C16010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01564537
WHO universal trial number (UTN)	U1111-1164-7646

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to determine whether the addition of oral ixazomib to the background therapy of lenalidomide and dexamethasone improves PFS in patients with RRMM.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	New Zealand: 67
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	France: 81
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Turkey: 7

Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Canada: 45
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Korea, Republic of: 6
Worldwide total number of subjects	722
EEA total number of subjects	384

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)	305
From 65 to 84 years	407
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 187 sites in Australia, Austria, Belgium, Canada, China, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Netherlands, New Zealand, Poland, Portugal, Romania, Russian Federation, Singapore, Spain, Sweden, Turkey, United Kingdom and US from 01 August 2012 to 08 February 2022.

Pre-assignment

Screening details:

Participants with a diagnosis of relapsed and/or refractory multiple myeloma were enrolled in 1 of 2 treatment groups: Ixazomib 4 mg or Ixazomib placebo-matching tablets in combination with lenalidomide, and dexamethasone.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ixazomib+ Lenalidomide + Dexamethasone

Arm description:

Ixazomib 4 mg, capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until progressive disease (PD) or unacceptable toxicity, whichever occurred first up to end of treatment (EOT) (up to approximately 42.9 months).

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	MLN9708, NINLARO®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules

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

Dosage and administration details:

Lenalidomide capsules

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

Dosage and administration details:

Dexamethasone tablets

Arm title	Placebo + Lenalidomide + Dexamethasone

Arm description:

Ixazomib placebo-matching capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first (up to approximately 41 months).

Arm type	Active comparator
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide capsules

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

Dosage and administration details:

Dexamethasone tablets

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

Dosage and administration details:

Ixazomib placebo-matching capsules.

Number of subjects in period 1	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone
Started	360	362
Intent-to-Treat (ITT) Population	360	362
Response Evaluable Population	345	348
Completed	259	263
Not completed	101	99
Consent withdrawn by subject	12	14
Site Terminated by Sponsor	1	-
Lost to follow-up	7	3
Reason not Specified	81	82

Baseline characteristics

Reporting groups	
Reporting group title	Ixazomib+ Lenalidomide + Dexamethasone
Reporting group description:	
Ixazomib 4 mg, capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until progressive disease (PD) or unacceptable toxicity, whichever occurred first up to end of treatment (EOT) (up to approximately 42.9 months).	
Reporting group title	Placebo + Lenalidomide + Dexamethasone
Reporting group description:	
Ixazomib placebo-matching capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first (up to approximately 41 months).	

Reporting group values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone	Total
Number of subjects	360	362	722
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.5	65.8	
standard deviation	± 9.13	± 9.70	-
Gender categorical Units: Subjects			
Male	207	202	409
Female	153	160	313
Age, Customized Units: Subjects			
≤65 years	168	176	344
>65-≤75 years	145	125	270
>75 years	47	61	108
Race/Ethnicity, Customized Units: Subjects			
White	312	303	615
Black or African American	7	6	13
Native Hawaiian/Other Pacific Islander	2	2	4
Asian	30	34	64
American Indian/Alaska native	0	1	1
Other	4	3	7
Race Not Reported	5	13	18
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	9	12	21
Not Hispanic or Latino	341	333	674
Ethnicity Not Reported	8	15	23
Missing	2	2	4

Stratification Factor: Lines of Prior Therapy Units: Subjects			
1 Line	212	213	425
2 or 3 Lines	148	149	297
Stratification Factor: Proteasome Inhibitor Units: Subjects			
Exposed	250	253	503
Naïve	110	109	219
Stratification Factor: International Staging System (ISS) Stag at Screening			
Stage I: Serum beta2-microglobulin <3.5 mg/L and albumin ≥3.5 g/dL; Stage II: Neither Stage I or III, meaning that either: beta2-microglobulin level ≥3.5 and <5.5 mg/L (with any albumin level), OR albumin <3.5 g/dL with beta2-microglobulin <3.5 mg/L; Stage III: Serum beta2-microglobulin ≥5.5 mg/L. Normal serum beta2-microglobulin: <3.0 mg/L; normal albumin: 3.5–5.0 g/dL.			
Units: Subjects			
Stage I or Stage II	314	318	632
Stage III	46	44	90

End points

End points reporting groups

Reporting group title	Ixazomib+ Lenalidomide + Dexamethasone

Reporting group description:

Ixazomib 4 mg, capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until progressive disease (PD) or unacceptable toxicity, whichever occurred first up to end of treatment (EOT) (up to approximately 42.9 months).

Reporting group title	Placebo + Lenalidomide + Dexamethasone

Reporting group description:

Ixazomib placebo-matching capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first (up to approximately 41 months).

Subject analysis set title	Safety Population: Ixazomib+ Lenalidomide + Dexamethasone
Subject analysis set type	Safety analysis

Subject analysis set description:

Ixazomib 4 mg, capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until progressive disease (PD) or unacceptable toxicity, whichever occurred first up to end of treatment (EOT) (up to approximately 42.9 months). Safety population included all randomized participants who received at least 1 dose of any study drug, regardless of their randomized treatment.

Subject analysis set title	Safety Population: Placebo + Lenalidomide + Dexamethasone
Subject analysis set type	Safety analysis

Subject analysis set description:

Ixazomib placebo-matching capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first (up to approximately 41 months). Safety population included all randomized participants who received at least 1 dose of any study drug, regardless of their randomized treatment.

Primary: Progression Free Survival (PFS) as Assessed by the Independent Review Committee (IRC)

End point title	Progression Free Survival (PFS) as Assessed by the Independent Review Committee (IRC)

End point description:

PFS: time from date of randomization to date of first documentation of PD or death due to any cause, whichever occurs first. Response including PD was assessed by IRC using IMWG response criteria. PD requires 1 of the following: Increase of ≥25% from nadir in: Serum M-component (absolute increase ≥0.5 g/dl); Urine M-component (absolute increase ≥ 200 mg/24 hours); In patients without measurable serum and urine M-protein levels difference between involved and uninvolved FLC levels (absolute increase > 10 mg/dl); Development of new or increase in size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease. Status evaluated every 4 weeks until PD was confirmed. Intent-to-Treat (ITT) population was defined as all randomized participants. 9999 indicates that the upper limit of 95% confidence interval was not estimable due to low number of participants with events.

End point type	Primary

End point timeframe:

From date of randomization until disease progression or death up to approximately 27 months (approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: months				
median (confidence interval 95%)	20.6 (17.02 to 9999)	14.7 (12.91 to 17.58)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ixazomib+ Lenalidomide + Dexamethasone v Placebo + Lenalidomide + Dexamethasone
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.742
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.666
upper limit	1.004

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time from the date of randomization to the date of death. Participants without documentation of death at the time of the analysis were censored at the date when they were last known to be alive. ITT population was defined as all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until death (up to approximately 97 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: months				
median (confidence interval 95%)	53.6 (49.25 to 62.95)	51.6 (44.78 to 59.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ixazomib+ Lenalidomide + Dexamethasone v Placebo + Lenalidomide + Dexamethasone
Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.495 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.784
upper limit	1.125

Notes:

[1] - HR:estimated from Cox Regression with stratification factors: prior therapies, proteasome inhibitor, and ISS Stage at Screening with treatment as factor in model. <1 hazard ratio for treatment=better prevention of death in drug arm vs control.

Secondary: Overall Response Rate (ORR) as Assessed by the IRC

End point title	Overall Response Rate (ORR) as Assessed by the IRC

End point description:

ORR was defined as the percentage of participants with Complete Response (CR) including stringent complete response (sCR), very good partial response (VGPR) and Partial Response (PR) assessed by the IRC using IMWG criteria. ITT population included all randomized participants. Percentages are rounded off to single decimal.

End point type	Secondary

End point timeframe:

Day 1 of each cycle (every 4 weeks) until disease progression up to approximately 27 months(approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: percentage of participants				
number (not applicable)	78.3	71.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in High-Risk Participants Carrying Deletion 17 [Del(17)]

End point title	Overall Survival in High-Risk Participants Carrying Deletion 17 [Del(17)]

End point description:

Overall survival is defined as the time from the date of randomization to the date of death. The high-risk participants whose myeloma carried del(17) subgroup was defined as the cases reported as positive for del(17) by the central laboratory combined with those cases that lacked a central laboratory result but with known del (17) by local laboratory. Participants without documentation of death at the time of the analysis were censored at the date when they were last known to be alive. Data is only reported high-risk participants with Del(17). ITT population was defined as all randomized participants. Overall number analyzed is the number of participants available for analysis at given timepoint.

End point type	Secondary

End point timeframe:

From the time of screening until disease progression and thereafter every 12 weeks until death or study termination (up to approximately 97 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: participants				
median (confidence interval 95%)	42.2 (27.56 to 56.74)	29.4 (16.99 to 44.22)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ixazomib+ Lenalidomide + Dexamethasone v Placebo + Lenalidomide + Dexamethasone
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.764 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.516
upper limit	1.626

Notes:

[2] - HR:estimated from Cox Regression with stratification factors: prior therapies, proteasome inhibitor, and ISS Stage at Screening with treatment as factor in model. <1 hazard ratio for treatment=better prevention of death in drug arm vs control.

Secondary: Percentage of Participants With Complete Response (CR) and Very Good Partial Response (VGPR) as Assessed by the IRC

End point title	Percentage of Participants With Complete Response (CR) and Very Good Partial Response (VGPR) as Assessed by the IRC

End point description:

Response was assessed by the IRC using International Myeloma Working Group (IMWG) Criteria. CR is defined as negative immunofixation on the serum and urine and; disappearance of any soft tissue plasmacytomas and; < 5% plasma cells in bone marrow. VGPR is defined as Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours. ITT population included all randomized participants. Percentages are rounded off to single decimal.

End point type	Secondary

End point timeframe:

Day 1 of each cycle (every 4 weeks) until disease progression up to approximately 27 months (approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: percentage of participants				
number (not applicable)	48.1	39.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) as Assessed by the IRC

End point title	Time to Progression (TTP) as Assessed by the IRC

End point description:

TTP was measured as the time in months from the first dose of study treatment to the date of the first documented progressive disease (PD) as assessed by the IRC using IMWG criteria. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

Day 1 of each cycle (every 4 weeks) until disease progression up to approximately 27 months (approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: months				
median (confidence interval 95%)	22.4 (18.73 to	17.6 (14.52 to		

27.66)	20.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was measured as the time in months from the date of first documentation of a confirmed response of PR or better (CR [including sCR] + PR+ VGPR) to the date of the first documented disease progression (PD) among participants who responded to the treatment. Response was assessed by the investigator using International Myeloma Working Group (IMWG) Criteria. Response-Evaluable population included all participants who received at least 1 dose of study drug, had measurable disease at baseline, and at least 1 post-baseline response assessment. Overall number analyzed is the number of participants available for analysis. 99999 Indicates CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Day 1 of each cycle (every 4 weeks) until disease progression up to approximately 38 months.

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	252		
Units: months				
median (confidence interval 95%)	26.0 (22.51 to 99999)	21.7 (17.77 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Eastern Cooperative Oncology Group (ECOG) performance score, laboratory values, vital sign measurements and reported adverse events (AEs) were collected and assessed to evaluate safety of therapy throughout the study. AE: any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. Serious adverse event (SAE) is an AE resulting in any

of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; or congenital anomaly; or a medically important event. Safety population.

End point type	Secondary

End point timeframe:

From the date of signing of the informed consent form through 30 days after the last dose of study drug up to approximately 115 months

End point values	Safety Population: Ixazomib+ Lenalidomide + Dexamethasone	Safety Population: Placebo + Lenalidomide + Dexamethasone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	361	359		
Units: participants				
number (not applicable)				
TEAEs (n=361, 359)	359	357		
SAEs (n=361, 359)	205	201		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Change From Baseline in Pain Response

End point title	Number of Participants with Change From Baseline in Pain Response

End point description:

Pain response was defined as 30% reduction from Baseline in Brief Pain Inventory-Short Form (BPI-SF) worst pain score over the last 24 hours without an increase in analgesic (oral morphine equivalents) use at 2 consecutive evaluations. The BPI-SF contains 15 items designed to capture the pain severity ("worst," "least," "average," and "now" [current pain]), pain location, medication to relieve the pain, and the interference of pain with various daily activities including general activity, mood, walking activity, normal work, relations with other people, sleep, and enjoyment of life. The pain severity items are rated on a 0 to 10 scale where: 0=no pain and 10=pain as bad as you can imagine and averaged for a total score of 0 (best) to 10 (Worst). ITT population included all randomized participants

End point type	Secondary

End point timeframe:

Baseline and end of treatment (EOT) (up to approximately 38 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: participants				
Baseline	345	351		

EOT	145	153		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) Questionnaire (EORTC-QLQ-C30)

End point title	Change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) Questionnaire (EORTC-QLQ-C30)

End point description:

EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer participants consisting of 15 domains: 1 global health status(GHS) scale, 5 functional scales(Physical,Role,Cognitive,Emotional,Social), and 9 symptom scales/items(Fatigue,Nausea and Vomiting,Pain,Dyspnea,Sleep Disturbance,Appetite Loss,Constipation,Diarrhea,Financial Impact). EORTC-QLQ-C30 GHS/QOL Scale is scored between 0-100; higher scores= better GHS/QOL. Negative changes from baseline = deterioration in QOL or functioning. Positive changes = improvement. Scores are linearly transformed to a 0-100 scale. High scores for the global and functional domains indicate higher quality of life or functioning. Higher scores on the symptom scales represent higher levels of symptomatology or problems. ITT population. Number analyzed: number of participants available for analysis at the given timepoint. 99999 indicate mean and/or SD were not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Baseline, EOT and follow-up (up to approximately 97 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: score on a scale				
arithmetic mean (standard deviation)				
Global Health Index: Baseline (n=355, 359)	58.4 (± 22.60)	56.4 (± 22.12)		
Global Health Index: End of Treatment (n=252, 257)	54.0 (± 21.15)	50.6 (± 23.65)		
Global Health Index: Follow up (n=0, 1)	99999 (± 99999)	66.7 (± 99999)		
Physical Functioning: Baseline (n=356, 359)	70.0 (± 21.74)	67.3 (± 23.54)		
Physical Functioning: EOT (n=253, 261)	-4.7 (± 22.61)	-6.2 (± 23.36)		
Physical Functioning: Last Follow-up (n=0, 1)	99999 (± 99999)	0.0 (± 99999)		
Role Functioning; Baseline (n=356, 360)	68.4 (± 28.75)	64.4 (± 30.24)		
Role Functioning: EOT (n=253, 261)	-8.6 (± 31.27)	-8.6 (± 32.90)		
Role Functioning: Last Follow-up (n=0, 1)	99999 (± 99999)	-16.7 (± 99999)		

Emotional Functioning: Baseline (n=355, 360)	75.1 (± 23.47)	75.3 (± 22.22)		
Emotional Functioning: EOT (n=251, 256)	-2.1 (± 20.09)	-6.1 (± 23.16)		
Emotional Functioning: Last Follow-up (n=0, 1)	99999 (± 99999)	-25.0 (± 99999)		
Cognitive Functioning: Baseline (n=355, 360)	81.9 (± 20.42)	81.6 (± 19.79)		
Cognitive Functioning: EOT (n=251, 256)	-7.6 (± 20.61)	-5.8 (± 22.24)		
Cognitive Functioning: Last Follow-up (n=0, 1)	99999 (± 99999)	-50.0 (± 99999)		
Social Functioning: Baseline (n=354, 360)	77.9 (± 26.07)	75.3 (± 26.47)		
Social Functioning: EOT (n=250, 256)	-6.9 (± 29.44)	-7.9 (± 29.37)		
Social Functioning: Last Follow-up (0, 1)	99999 (± 99999)	0.0 (± 99999)		
Fatigue: Baseline (n=356, 360)	38.4 (± 23.98)	39.5 (± 25.14)		
Fatigue: EOT (n=253, 261)	6.0 (± 25.38)	6.7 (± 26.61)		
Fatigue: Last Follow-up (n=0, 1)	99999 (± 99999)	22.2 (± 99999)		
Pain: Baseline (n=356, 360)	38.0 (± 28.30)	38.5 (± 30.99)		
Pain: EOT (n=253, 261)	2.7 (± 26.65)	3.8 (± 30.07)		
Pain: Last Follow-up (n=0, 1)	99999 (± 99999)	0.0 (± 99999)		
Nausea and Vomiting: Baseline (n=356, 360)	5.0 (± 12.89)	6.0 (± 13.31)		
Nausea and Vomiting: EOT (n=252, 261)	3.4 (± 16.85)	0.6 (± 19.22)		
Nausea and Vomiting: Last Follow-up (n=0, 1)	99999 (± 99999)	33.3 (± 99999)		
Dyspnea: Baseline (n=356, 360)	21.2 (± 26.74)	23.7 (± 26.68)		
Dyspnea: EOT (n=252, 261)	5.7 (± 31.04)	2.3 (± 27.33)		
Dyspnea: Last Follow-up (n=0, 1)	99999 (± 99999)	1 (± 99999)		
Insomnia: Baseline (n=356, 360)	27.4 (± 31.04)	30.5 (± 31.59)		
Insomnia: EOT (n=252, 260)	0.9 (± 31.41)	-0.5 (± 33.26)		
Insomnia: Last Follow-up (n=0, 1)	99999 (± 99999)	33.3 (± 99999)		
Appetite Loss: Baseline (n=356, 360)	16.9 (± 25.70)	15.3 (± 25.21)		
Appetite Loss: EOT (n=253, 260)	4.7 (± 31.49)	6.5 (± 28.47)		
Appetite Loss: Last Follow-up (n=0, 1)	99999 (± 99999)	0.0 (± 99999)		
Constipation: Baseline (n=355, 360)	12.2 (± 22.58)	13.5 (± 24.30)		
Constipation: EOT (n= 249, 259)	-1.3 (± 26.57)	2.2 (± 27.05)		
Constipation: Last Follow-up (n=0, 1)	99999 (± 99999)	33.3 (± 99999)		
Diarrhea: Baseline (n=355, 360)	6.3 (± 16.38)	8.1 (± 18.49)		
Diarrhea: EOT (n=250, 256)	17.2 (± 31.08)	10.8 (± 31.53)		
Diarrhea: Last Follow-up (n=0, 1)	99999 (± 99999)	0.0 (± 99999)		
Financial Difficulties: Baseline (n=352, 360)	16.7 (± 26.15)	18.6 (± 28.30)		
Financial Difficulties: EOT (n=250, 256)	0.5 (± 20.69)	1.3 (± 26.54)		
Financial Difficulties: Last Follow-up (n=0, 1)	99999 (± 99999)	-33.3 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Multiple Myeloma Module (QLQ-MY-20)

End point title	Change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Multiple Myeloma Module (QLQ-MY-20)

End point description:

The EORTC-QLQ-MY-20 is a patient-completed, 20-question quality of life questionnaire that has 4 independent subscales, 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment). The participant answers questions about their health during the past week using a 4-point scale where 1=Not at All to 4=Very Much. A negative change from Baseline indicates improvement. Scores are linearly transformed to a 0-100 scale. Higher scores on the symptom scales (e.g. Disease Symptoms, Side Effects of Treatment) represent higher levels of symptomatology or problems. High scores for Body Image and Future Perspective represent better quality of life or functioning. ITT population included all randomized participants. 99999 indicates SD was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Baseline, EOT and follow-up (up to approximately 97 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	362		
Units: score on a scale				
arithmetic mean (standard deviation)				
Disease Symptoms: Baseline (n=354, 359)	29.71 (± 20.850)	30.41 (± 23.072)		
Disease Symptoms: End of Treatment (n=250, 257)	-2.35 (± 20.752)	-2.58 (± 21.372)		
Disease Symptoms: Last Follow-up (n=1, 1)	1.11 (± 99999)	99999 (± 99999)		
Side Effects of Treatment: Baseline (n=354, 359)	17.23 (± 14.289)	17.97 (± 14.682)		
Side Effects of Treatment: EOT (n=249, 255)	4.52 (± 14.435)	4.43 (± 13.955)		
Side Effects of Treatment: Last Follow-up (n=0, 1)	99999 (± 99999)	37.04 (± 99999)		
Body Image: Baseline (n=353, 359)	78.00 (± 29.259)	79.48 (± 27.233)		
Body Image: EOT (n=245, 254)	-0.27 (± 29.102)	-5.38 (± 29.368)		

Body Image: Last Follow-up (n=0, 1)	99999 (± 99999)	-33.3 (± 99999)		
Future Perspective: Baseline (n=353, 359)	56.99 (± 25.170)	60.26 (± 25.064)		
Future Perspective: EOT (n=248, 255)	2.76 (± 22.90)	-2.75 (± 22.842)		
Future Perspective: Last Follow-up	99999 (± 99999)	-11.11 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in High-Risk Participants

End point title	OS in High-Risk Participants

End point description:

Overall survival (OS) is defined as the time from the date of randomization to the date of death. High-risk participants are defined as participants carrying cytogenic abnormalities: del(17), translocation t(4;14), or t(14;16) as reported by the central laboratory combined with those cases that lacked a central laboratory result but with known del (17), t(4;14), or t(14;16) by local laboratory. Cytogenetic abnormalities of del(13) and +1q are no longer considered to be high-risk abnormalities and are not included in the analysis. Participants without documentation of death at the time of the analysis were censored at the date when they were last known to be alive. Data is only reported high-risk participants. ITT population included all randomized participants. Overall number analyzed is the number of participants available for analysis.

End point type	Secondary

End point timeframe:

From the time of screening until disease progression and thereafter every 12 weeks until death or study termination (up to approximately 97 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	62		
Units: months				
median (confidence interval 95%)	46.9 (34.04 to 64.53)	30.9 (24.77 to 42.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration Over Time for Ixazomib

End point title	Plasma Concentration Over Time for Ixazomib

End point description:

Safety population is defined as all subjects who received at least 1 dose of any study drug. Overall number analyzed is the number of participants available for analysis. Number analyzed is the number of

participants available for analysis at the given timepoint. 9999 indicates the SD was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Pre-dose and post-dose at multiple timepoints up to Cycle 10 Day 1 (each cycle length = 28 days)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	5		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=1, 0)	4.79 (± 9999)	9999 (± 9999)		
Cycle 1 Day 1, 1 Hour Post-Dose (n=330, 4)	36.3 (± 31.3)	0 (± 0)		
Cycle 1 Day 1, 4 Hours Post-Dose (n=321, 4)	15.6 (± 11.1)	0 (± 0)		
Cycle 1 Day 14, Pre-Dose (n=335, 4)	6.83 (± 10.5)	0 (± 0)		
Cycle 2 Day 1, Pre-Dose (n=331, 5)	2.4 (± 2.4)	0 (± 0)		
Cycle 2 Day 14, Pre-Dose (n=324, 5)	7.12 (± 8.44)	0 (± 0)		
Cycle 3 Day 1, Pre-Dose (n=329, 5)	2.48 (± 1.69)	0 (± 0)		
Cycle 4 Day 1, Pre-Dose (n=319, 4)	2.41 (± 1.35)	0 (± 0)		
Cycle 5 Day 1, Pre-Dose (n=307, 4)	2.42 (± 1.49)	0 (± 0)		
Cycle 6 Day 1, Pre-Dose (n=290, 4)	2.57 (± 3.89)	0 (± 0)		
Cycle 7 Day 1, Pre-Dose (n=279, 3)	2.71 (± 4.79)	0 (± 0)		
Cycle 8 Day 1, Pre-Dose (n=268, 2)	2.37 (± 1.47)	0 (± 0)		
Cycle 9 Day 1, Pre-Dose (n=262, 4)	2.51 (± 2.13)	0 (± 0)		
Cycle 10 Day 1, Pre-Dose (n=239, 2)	2.82 (± 5.98)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in High-Risk Participants

End point title	PFS in High-Risk Participants

End point description:

Progression Free Survival (PFS) is defined as the time from the date of randomization to the date of first documentation of disease progression or death due to any cause, whichever occurs first. Response was assessed by independent review committee (IRC) using IMWG response criteria. High-risk participants are defined as participants carrying cytogenic abnormalities: del(17), translocation t(4;14), or t(14;16) as reported by the central laboratory combined with those cases that lacked a central laboratory result but with known del (17), t(4;14), or t(14;16) by local laboratory. Cytogenetic abnormalities of del(13) and +1q are no longer considered to be high-risk abnormalities and are not included in the analysis. Participants from the ITT population, all randomized participants, with cytogenic abnormalities. 99999 indicates upper limit of 95% CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

From date of randomization until disease progression or death up to approximately 38 months. (approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	62		
Units: months				
median (confidence interval 95%)	18.7 (13.24 to 99999)	9.3 (7.36 to 15.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate in Participants Defined by Polymorphism

End point title	Overall Response Rate in Participants Defined by Polymorphism

End point description:

Data is reported for percentage of participants defined by polymorphism defined by polymorphisms in proteasome genes, such as polymorphism P11A in PSMB1 gene. ITT population included all randomized participants. Overall number analyzed is the number of participants available with data. Percentages are rounded off to single decimal.

End point type	Secondary

End point timeframe:

Day 1 of each cycle (every 4 weeks) until disease progression up to approximately 27 months (approximate median follow-up 15 months)

End point values	Ixazomib+ Lenalidomide + Dexamethasone	Placebo + Lenalidomide + Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: percentage of participants				
number (confidence interval 95%)	80.3 (72.0 to 87.1)	75.7 (66.8 to 83.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ixazomib+ Lenalidomide + Dexamethasone v Placebo + Lenalidomide + Dexamethasone

Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.332 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.45

Notes:

[3] - Odds ratio is from logistic regression model with prognostic factors: prior therapies, proteasome inhibitor,and ISS Stage at Screening. Odds ratio>1 favors Ixazomib.

[4] - P-value is from Cochran-Mantel-Haenszel stratified by: prior therapies, proteasome inhibitor, and ISS Stage at Screening.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of signing of the informed consent form through 30 days after the last dose of study drug up to approximately 115 months

Adverse event reporting additional description:

The investigator had to document any occurrence of adverse events including abnormal laboratory findings. Any event spontaneously reported by the participant or observed by investigator was recorded, irrespective of the relation to study treatment. Safety population: all randomized participants who received at least 1 dose of any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Placebo + Lenalidomide + Dexamethasone

Reporting group description:

Ixazomib placebo-matching capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first (up to approximately 41 months).

Reporting group title	Ixazomib+ Lenalidomide + Dexamethasone

Reporting group description:

Ixazomib 4 mg, capsules, orally, once, on Days 1, 8 and 15; plus lenalidomide 25 mg, orally, once, on Days 1 through 21; and dexamethasone 40 mg, orally, once, on Days 1, 8, 15 and 22 of a 28-day cycle for multiple cycles until PD or unacceptable toxicity, whichever occurred first up to EOT (up to approximately 42.9 months).

Serious adverse events	Placebo + Lenalidomide + Dexamethasone	Ixazomib+ Lenalidomide + Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	202 / 359 (56.27%)	205 / 361 (56.79%)	
number of deaths (all causes)	251	250	
number of deaths resulting from adverse events	30	22	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 359 (0.28%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 359 (0.84%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder adenocarcinoma stage unspecified			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	2 / 359 (0.56%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	7 / 359 (1.95%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	1 / 10	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			

subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neuroendocrine tumour			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile squamous cell carcinoma			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	3 / 359 (0.84%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 3	
Plasmacytoma			
subjects affected / exposed	0 / 359 (0.00%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobular breast carcinoma in situ			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	7 / 359 (1.95%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	6 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis superficial			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Performance status decreased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 359 (0.84%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Chills			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	18 / 359 (5.01%)	12 / 361 (3.32%)	
occurrences causally related to treatment / all	6 / 20	9 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue inflammation			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's cyst			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 359 (0.56%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Organising pneumonia			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 359 (0.84%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	4 / 359 (1.11%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	9 / 359 (2.51%)	7 / 361 (1.94%)	
occurrences causally related to treatment / all	9 / 9	6 / 8	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pulmonary hypertension			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary microemboli			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Confusional state			
subjects affected / exposed	2 / 359 (0.56%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 359 (0.28%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	2 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	1 / 359 (0.28%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	4 / 359 (1.11%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 359 (0.56%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (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	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	5 / 359 (1.39%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 359 (0.84%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	7 / 359 (1.95%)	6 / 361 (1.66%)	
occurrences causally related to treatment / all	6 / 8	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 359 (0.84%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	1 / 3	0 / 2	
Cardiac failure			
subjects affected / exposed	6 / 359 (1.67%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	6 / 7	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 359 (0.84%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 359 (0.00%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 359 (0.56%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	1 / 2	0 / 1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diastolic dysfunction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Trifascicular block			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acute polyneuropathy			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebrovascular accident			

subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral small vessel ischaemic disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	4 / 359 (1.11%)	6 / 361 (1.66%)	
occurrences causally related to treatment / all	2 / 5	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 359 (0.00%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperviscosity syndrome			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	9 / 359 (2.51%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	6 / 9	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	10 / 359 (2.79%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	22 / 31	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 359 (0.56%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 359 (1.67%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	6 / 6	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 359 (0.28%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	7 / 359 (1.95%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	6 / 8	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 359 (0.84%)	12 / 361 (3.32%)	
occurrences causally related to treatment / all	2 / 3	8 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	2 / 359 (0.56%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	5 / 359 (1.39%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (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	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cutaneous vasculitis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 359 (1.67%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	3 / 8	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atonic urinary bladder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral meatus stenosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral haemorrhage			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic bladder			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Toxic goitre			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	8 / 359 (2.23%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	4 / 359 (1.11%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	2 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 359 (2.79%)	6 / 361 (1.66%)	
occurrences causally related to treatment / all	5 / 10	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (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	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	3 / 359 (0.84%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Endocarditis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 359 (0.56%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Candida pneumonia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter colitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (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	5 / 359 (1.39%)	8 / 361 (2.22%)	
occurrences causally related to treatment / all	0 / 6	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 359 (0.84%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	1 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	3 / 359 (0.84%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	3 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis caliciviral			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 359 (0.28%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 359 (0.28%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia escherichia			

subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	46 / 359 (12.81%)	47 / 361 (13.02%)	
occurrences causally related to treatment / all	41 / 65	26 / 59	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumococcal sepsis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	2 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Moraxella infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			

subjects affected / exposed	3 / 359 (0.84%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 359 (1.11%)	6 / 361 (1.66%)	
occurrences causally related to treatment / all	2 / 4	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteus infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
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	3 / 359 (0.84%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 359 (0.56%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia moraxella			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			

subjects affected / exposed	7 / 359 (1.95%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 359 (0.28%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 359 (1.39%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	3 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	5 / 359 (1.39%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	2 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sinusitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 359 (0.84%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 359 (1.67%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	0 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
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 / 359 (0.56%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral leishmaniasis			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 359 (0.56%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 359 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			

subjects affected / exposed	1 / 359 (0.28%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 359 (0.84%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 359 (0.00%)	2 / 361 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 359 (0.28%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Lenalidomide + Dexamethasone	Ixazomib+ Lenalidomide + Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 359 (95.26%)	350 / 361 (96.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 359 (7.52%)	29 / 361 (8.03%)	
occurrences (all)	36	34	
Deep vein thrombosis			
subjects affected / exposed	18 / 359 (5.01%)	11 / 361 (3.05%)	
occurrences (all)	18	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	66 / 359 (18.38%)	62 / 361 (17.17%)	
occurrences (all)	91	85	
Influenza like illness			

subjects affected / exposed	15 / 359 (4.18%)	25 / 361 (6.93%)	
occurrences (all)	22	39	
Oedema peripheral			
subjects affected / exposed	76 / 359 (21.17%)	97 / 361 (26.87%)	
occurrences (all)	114	152	
Peripheral swelling			
subjects affected / exposed	7 / 359 (1.95%)	20 / 361 (5.54%)	
occurrences (all)	8	23	
Pyrexia			
subjects affected / exposed	71 / 359 (19.78%)	55 / 361 (15.24%)	
occurrences (all)	126	111	
Fatigue			
subjects affected / exposed	103 / 359 (28.69%)	113 / 361 (31.30%)	
occurrences (all)	150	183	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	16 / 359 (4.46%)	20 / 361 (5.54%)	
occurrences (all)	25	23	
Cough			
subjects affected / exposed	65 / 359 (18.11%)	73 / 361 (20.22%)	
occurrences (all)	99	116	
Dysphonia			
subjects affected / exposed	21 / 359 (5.85%)	7 / 361 (1.94%)	
occurrences (all)	23	7	
Dyspnoea			
subjects affected / exposed	40 / 359 (11.14%)	44 / 361 (12.19%)	
occurrences (all)	45	48	
Dyspnoea exertional			
subjects affected / exposed	24 / 359 (6.69%)	17 / 361 (4.71%)	
occurrences (all)	29	19	
Oropharyngeal pain			
subjects affected / exposed	21 / 359 (5.85%)	16 / 361 (4.43%)	
occurrences (all)	22	19	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	23 / 359 (6.41%)	18 / 361 (4.99%)	
occurrences (all)	32	19	
Depression			
subjects affected / exposed	18 / 359 (5.01%)	19 / 361 (5.26%)	
occurrences (all)	20	23	
Insomnia			
subjects affected / exposed	106 / 359 (29.53%)	82 / 361 (22.71%)	
occurrences (all)	123	105	
Mood altered			
subjects affected / exposed	21 / 359 (5.85%)	12 / 361 (3.32%)	
occurrences (all)	25	18	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	28 / 359 (7.80%)	26 / 361 (7.20%)	
occurrences (all)	100	70	
Platelet count decreased			
subjects affected / exposed	22 / 359 (6.13%)	36 / 361 (9.97%)	
occurrences (all)	39	64	
Weight decreased			
subjects affected / exposed	28 / 359 (7.80%)	36 / 361 (9.97%)	
occurrences (all)	35	45	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	40 / 359 (11.14%)	35 / 361 (9.70%)	
occurrences (all)	64	43	
Contusion			
subjects affected / exposed	22 / 359 (6.13%)	23 / 361 (6.37%)	
occurrences (all)	27	29	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	19 / 359 (5.29%)	17 / 361 (4.71%)	
occurrences (all)	22	26	
Nervous system disorders			
Dizziness			

subjects affected / exposed	43 / 359 (11.98%)	58 / 361 (16.07%)	
occurrences (all)	51	72	
Dysgeusia			
subjects affected / exposed	15 / 359 (4.18%)	23 / 361 (6.37%)	
occurrences (all)	17	28	
Headache			
subjects affected / exposed	56 / 359 (15.60%)	53 / 361 (14.68%)	
occurrences (all)	72	76	
Neuropathy peripheral			
subjects affected / exposed	26 / 359 (7.24%)	35 / 361 (9.70%)	
occurrences (all)	34	51	
Paraesthesia			
subjects affected / exposed	19 / 359 (5.29%)	33 / 361 (9.14%)	
occurrences (all)	23	55	
Peripheral sensory neuropathy			
subjects affected / exposed	61 / 359 (16.99%)	88 / 361 (24.38%)	
occurrences (all)	80	131	
Tremor			
subjects affected / exposed	38 / 359 (10.58%)	22 / 361 (6.09%)	
occurrences (all)	45	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	105 / 359 (29.25%)	123 / 361 (34.07%)	
occurrences (all)	182	203	
Leukopenia			
subjects affected / exposed	19 / 359 (5.29%)	28 / 361 (7.76%)	
occurrences (all)	33	60	
Neutropenia			
subjects affected / exposed	99 / 359 (27.58%)	112 / 361 (31.02%)	
occurrences (all)	297	359	
Thrombocytopenia			
subjects affected / exposed	44 / 359 (12.26%)	95 / 361 (26.32%)	
occurrences (all)	91	221	
Eye disorders			
Cataract			

subjects affected / exposed	61 / 359 (16.99%)	50 / 361 (13.85%)	
occurrences (all)	73	64	
Vision blurred			
subjects affected / exposed	18 / 359 (5.01%)	26 / 361 (7.20%)	
occurrences (all)	18	27	
Dry eye			
subjects affected / exposed	6 / 359 (1.67%)	22 / 361 (6.09%)	
occurrences (all)	6	22	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	36 / 359 (10.03%)	37 / 361 (10.25%)	
occurrences (all)	48	46	
Abdominal pain upper			
subjects affected / exposed	17 / 359 (4.74%)	26 / 361 (7.20%)	
occurrences (all)	19	34	
Constipation			
subjects affected / exposed	99 / 359 (27.58%)	125 / 361 (34.63%)	
occurrences (all)	128	168	
Vomiting			
subjects affected / exposed	47 / 359 (13.09%)	93 / 361 (25.76%)	
occurrences (all)	77	185	
Dry mouth			
subjects affected / exposed	25 / 359 (6.96%)	16 / 361 (4.43%)	
occurrences (all)	27	18	
Dyspepsia			
subjects affected / exposed	31 / 359 (8.64%)	33 / 361 (9.14%)	
occurrences (all)	41	44	
Nausea			
subjects affected / exposed	83 / 359 (23.12%)	114 / 361 (31.58%)	
occurrences (all)	125	158	
Diarrhoea			
subjects affected / exposed	153 / 359 (42.62%)	186 / 361 (51.52%)	
occurrences (all)	343	502	
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	13 / 359 (3.62%)	22 / 361 (6.09%)	
occurrences (all)	16	26	
Hyperhidrosis			
subjects affected / exposed	18 / 359 (5.01%)	14 / 361 (3.88%)	
occurrences (all)	20	14	
Pruritus			
subjects affected / exposed	32 / 359 (8.91%)	45 / 361 (12.47%)	
occurrences (all)	44	64	
Rash macular			
subjects affected / exposed	29 / 359 (8.08%)	26 / 361 (7.20%)	
occurrences (all)	40	42	
Rash maculo-papular			
subjects affected / exposed	15 / 359 (4.18%)	34 / 361 (9.42%)	
occurrences (all)	24	67	
Rash			
subjects affected / exposed	11 / 359 (3.06%)	20 / 361 (5.54%)	
occurrences (all)	12	24	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	16 / 359 (4.46%)	22 / 361 (6.09%)	
occurrences (all)	22	30	
Arthralgia			
subjects affected / exposed	71 / 359 (19.78%)	79 / 361 (21.88%)	
occurrences (all)	108	143	
Back pain			
subjects affected / exposed	82 / 359 (22.84%)	97 / 361 (26.87%)	
occurrences (all)	99	130	
Bone pain			
subjects affected / exposed	34 / 359 (9.47%)	33 / 361 (9.14%)	
occurrences (all)	46	41	
Muscle spasms			
subjects affected / exposed	102 / 359 (28.41%)	70 / 361 (19.39%)	
occurrences (all)	152	110	
Muscular weakness			

subjects affected / exposed	28 / 359 (7.80%)	21 / 361 (5.82%)	
occurrences (all)	34	28	
Musculoskeletal chest pain			
subjects affected / exposed	39 / 359 (10.86%)	33 / 361 (9.14%)	
occurrences (all)	46	42	
Neck pain			
subjects affected / exposed	21 / 359 (5.85%)	14 / 361 (3.88%)	
occurrences (all)	25	16	
Pain in extremity			
subjects affected / exposed	41 / 359 (11.42%)	54 / 361 (14.96%)	
occurrences (all)	52	72	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	83 / 359 (23.12%)	97 / 361 (26.87%)	
occurrences (all)	162	191	
Bronchitis			
subjects affected / exposed	53 / 359 (14.76%)	76 / 361 (21.05%)	
occurrences (all)	83	143	
Conjunctivitis			
subjects affected / exposed	10 / 359 (2.79%)	34 / 361 (9.42%)	
occurrences (all)	10	37	
Gastroenteritis			
subjects affected / exposed	17 / 359 (4.74%)	26 / 361 (7.20%)	
occurrences (all)	19	34	
Herpes zoster			
subjects affected / exposed	7 / 359 (1.95%)	20 / 361 (5.54%)	
occurrences (all)	9	22	
Influenza			
subjects affected / exposed	26 / 359 (7.24%)	27 / 361 (7.48%)	
occurrences (all)	29	35	
Lower respiratory tract infection			
subjects affected / exposed	18 / 359 (5.01%)	16 / 361 (4.43%)	
occurrences (all)	22	22	
Nasopharyngitis			
subjects affected / exposed	86 / 359 (23.96%)	90 / 361 (24.93%)	
occurrences (all)	163	193	

Oral candidiasis			
subjects affected / exposed	19 / 359 (5.29%)	17 / 361 (4.71%)	
occurrences (all)	23	21	
Pharyngitis			
subjects affected / exposed	22 / 359 (6.13%)	16 / 361 (4.43%)	
occurrences (all)	30	19	
Pneumonia			
subjects affected / exposed	33 / 359 (9.19%)	46 / 361 (12.74%)	
occurrences (all)	40	62	
Respiratory tract infection			
subjects affected / exposed	30 / 359 (8.36%)	23 / 361 (6.37%)	
occurrences (all)	38	31	
Sinusitis			
subjects affected / exposed	21 / 359 (5.85%)	25 / 361 (6.93%)	
occurrences (all)	28	43	
Urinary tract infection			
subjects affected / exposed	34 / 359 (9.47%)	43 / 361 (11.91%)	
occurrences (all)	58	77	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 359 (11.70%)	51 / 361 (14.13%)	
occurrences (all)	52	63	
Hyperglycaemia			
subjects affected / exposed	23 / 359 (6.41%)	18 / 361 (4.99%)	
occurrences (all)	34	31	
Hypocalcaemia			
subjects affected / exposed	21 / 359 (5.85%)	24 / 361 (6.65%)	
occurrences (all)	41	35	
Hypokalaemia			
subjects affected / exposed	51 / 359 (14.21%)	60 / 361 (16.62%)	
occurrences (all)	71	100	
Hypomagnesaemia			
subjects affected / exposed	26 / 359 (7.24%)	18 / 361 (4.99%)	
occurrences (all)	47	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	Amendment 1: The purposes of this amendment are to: • Clarify the time of collection for EORTC-QLQ-C30, EQ-5D, and MY-20 outcome measures • Change the term from 'progressive disease confirmation' to 'progressive disease review' • Clarify the pharmacokinetics schedule with regard to study dosing and requirements for fasting • Clarify the duration of collection and evaluation of new or worsening of existing selected skeletal events from baseline through the last survival assessment to be in line with the Schedule of Events (SOE) • Clarify the use of aspirin for prophylactic anticoagulation and subjects with deep vein thrombosis can take low molecular weight heparin in the inclusion criteria • Clarify the acceptable grade for recovery from effects of prior chemotherapy, reference to hepatitis B and C virus infections and comorbid systemic illness or other severe concurrent disease in the exclusion criteria • Clarify dose modification procedures and the toxicity recovery before beginning the next cycle of treatment • Clarify the procedures for dose modifications due to nonhematologic toxicity judged to be related to study drug and the timing for collection of concomitant medications • Update the clinical management of thrombocytopenia to include thrombotic thrombocytopenic purpura (TTP) • Clarify the collection of pain assessments on the BPI-SF and 24-hour analgesic forms and bone marrow aspirate is used to confirm complete response and/or progressive disease • Clarify that plasma concentrations will be measured using a validated LC/MS/MS assay and remove optional PK collection at the time of SAEs • Clarify that radiographic disease assessments are to be performed every 8 weeks during PFS follow-up period • Clarify collection and reporting requirements for SAEs related to study drug during posttreatment follow-up and assessments to be performed for End of Treatment visit are listed in SOE • Add an analysis for pain response • Update definition of pain progression

08 July 2014	Amendment 3: The purposes of this amendment are to: • Update the statistical and quantitative analyses sections to include the assumptions on PFS for sample size calculation and additional IA • Remove the non-inferential test on PFS at the original planned second IA • Reclassify of the secondary biomarker objectives to exploratory objectives • Update the study overview diagram to remove subsequent anti-neoplastic therapy as a grounds for treatment discontinuation • Clarify the timing of the EQ-5D Health Questionnaire and skeletal survey • Clarify the pharmacokinetic sampling schedule • Remove assessments of specific gene mutations of the P13K pathway and indicate that similar analyses will be done in tumor samples from patients who initially responded to therapy and subsequently relapsed • Clarify the PFS and OS assessment intervals in the Overview of the Study Design section to be consistent with the SOE • Update the inclusion criteria to align with current standard informed consent form (ICF) contraception durations • Clarify the gastrointestinal and metabolic adverse event severities for dexamethasone-related treatment modification guidelines • Clarify the M-protein and free light chain to be followed for response assessment according to IMWG criteria • Update the criteria for completion of treatment • Indicate that the investigator is required to submit the rationale for discontinuing a patient from study treatment • Clarify that the ITT population is used for patient-reported outcome assessments • Replace “time to pain response” with “duration of pain response” and indicate how data for this response will be summarized • Add that the IDMC will receive reports of all cases of new primary malignancies during the study • Update the procedures for reporting drug exposure during pregnancy to be consistent throughout the protocol • Clarify the IMWG response criteria version used for the study and clarify VGPR in terms of plasmacytoma
11 December 2016	Amendment 6: The purposes of this amendment are to: •Remove mention of the Safety Management Attachment, which no longer exists •Discontinue the PFS follow-up period and all efficacy response assessments, including laboratory assessments, for protocol purposes because PFS significance has been met in the study •Remove the futility boundary for OS at the third interim analysis and note that the actual efficacy boundaries may be adjusted if the actual number of events does not correspond to the projected number of events in the remaining analyses •Update the excluded concomitant medication information to reflect recent population pharmacokinetics (PK) analyses and drug-drug interaction study results from Study C16009 demonstrating that cytochrome P450 inhibitors do not affect MLN9708 PK •Clarify the management of rash, including adding a table of steroid equivalent doses •Clarify the management of overdose •Clarify the instructions for study drug dispensing •Clarify the procedure for performing the physical examination •Clarify when central laboratory results must be reviewed before initiating the next treatment cycle •Note that PK sample collection for the study has now been completed for all participants •Add an email address for reporting adverse events (AEs) and serious AEs in Japan •Clarify the monitoring of AEs and period of observation •Update the procedures for product complaints to include instructions for reporting medication errors and overdose •Clarify the definition of closure of the study

07 January 2021	Amendment 8: The purposes of this amendment are to: 1. Clarify the study objectives as of Amendment 8. 2. Clarify the study endpoints as of Amendment 8. 3. Clarify that the final analysis data cutoff has been conducted and the study is considered complete for statistical analysis purposes. 4. Add language to clarify ongoing treatment of participants—participants still receiving study treatment will stay on their assigned study regimen. Participants should be moved off study and onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. 5. Discontinue all remaining efficacy assessments (eg, OS, Quality of Life) and clarify ongoing safety laboratory evaluations. 6. Discontinue the OS follow-up period. 7. Revise information regarding the interim analyses. 8. Update language about the management of clinical events in participants receiving ixazomib. 9. Clarify the procedures for storage, handling, and accountability. 10. Add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic). 11. Add language requiring all participants to reconsent. 12. Clarify the definition of Completion of Treatment. 13. Clarify the definition of Completion of Study. 14. Update the procedures for SAE reporting. 15. Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported