



Clinical trial results:

An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

Summary

EudraCT number	2013-003113-17
Trial protocol	SE GR PL
Global end of trial date	29 June 2018

Results information

Result version number	v1 (current)
This version publication date	10 July 2019
First version publication date	10 July 2019

Trial information

Trial identification

Sponsor protocol code	C16020
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02046070
WHO universal trial number (UTN)	U1111-1158-2714

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Sponsor organisation address	40 Landsdowne Street, Cambridge, United States, MA 02139
Public contact	Medical Director, Clinical Science, Takeda Oncology, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda Oncology, +1 877-825-3327, clinicaltrialregistry@tpna.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	29 June 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase 2, multicenter, open-label study in patients with Newly Diagnosed Multiple Myeloma (NDMM) who have not received prior systemic treatment for multiple myeloma (MM) and who are ineligible for high-dose therapy (HDT)-stem cell transplantation (SCT) due to age (ie, ≥ 65 years) or comorbid disease(s) or with Relapsed and/or Refractory Multiple Myeloma (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	05 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	45 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Greece: 52
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	148
EEA total number of subjects	119

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)	43
From 65 to 84 years	102
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 23 investigative sites in Australia, Greece, Poland, Sweden and the United States from 05 March 2014 to 29 June 2018.

Pre-assignment

Screening details:

Participants with NDMM were enrolled in 1 of 2 arms to receive 4.0 mg ixazomib in combination with 300 or 400 mg cyclophosphamide and 40 mg dexamethasone (CCd); participants with RRMM were enrolled in 1 arm to receive ixazomib 4.0 mg CCd. All arms included a safety lead-in cohort for pharmacokinetics (PK) analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ixazomib 4.0 mg + CYC 300 mg/m² + DEX 40 mg (NDMM)

Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

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

Dosage and administration details:

Cyclophosphamide tablets.

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	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Arm title	Ixazomib 4.0 mg + CYC 400 mg/m² + DEX 40 mg (NDMM)
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Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

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

Dosage and administration details:

Cyclophosphamide tablets.

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	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Arm title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
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Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.

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

Dosage and administration details:

Cyclophosphamide tablets.

Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	MLN9708
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib capsules.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use
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Dosage and administration details:

Dexamethasone tablets.

Number of subjects in period 1	Ixazomib 4.0 mg + CYC 300 mg/m² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 300 mg/m² + DEX 40 mg (RRMM)
Started	36	34	78
Completed	4	6	8
Not completed	32	28	70
Consent withdrawn by subject	1	2	6
Adverse event, non-fatal	8	10	17
Progressive Disease	18	11	40
Study Terminated by Sponsor	1	1	1
Reason not Specified	4	4	6

Baseline characteristics

Reporting groups

Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)
Reporting group description:	
Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.	
Reporting group title	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)
Reporting group description:	
Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.	
Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
Reporting group description:	
Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.	

Reporting group values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
Number of subjects	36	34	78
Age categorical			
Units: Subjects			
Adults (18-64 years)	0	2	41
From 65-84 years	34	32	36
85 years and over	2	0	1
Age Continuous			
Units: years			
arithmetic mean	73.4	74.1	63.5
standard deviation	± 5.48	± 5.80	± 9.85
Sex: Female, Male			
Units: Subjects			
Female	21	16	37
Male	15	18	41
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	35	33	75
Unknown or Not Reported	0	1	3
Race/Ethnicity, Customized			
Units: Subjects			
White	35	34	74
Other	1	0	2
Asian	0	0	1

Black or African American	0	0	1
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Height Units: centimeters (cm) arithmetic mean standard deviation	163.5 ± 11.35	163.5 ± 12.47	165.9 ± 10.47
Weight Units: kilograms (kg) arithmetic mean standard deviation	73.6 ± 11.8	73.0 ± 17.54	78.1 ± 16.80
Body Surface Area (BSA)			
BSA = square root (height(cm) x weight (kg) / 3600.			
Units: meters squared (m ²) arithmetic mean standard deviation	1.8 ± 0.17	1.8 ± 0.26	1.9 ± 0.23

Reporting group values	Total		
Number of subjects	148		
Age categorical Units: Subjects			
Adults (18-64 years)	43		
From 65-84 years	102		
85 years and over	3		
Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	74		
Male	74		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	143		
Unknown or Not Reported	4		
Race/Ethnicity, Customized Units: Subjects			
White	143		
Other	3		
Asian	1		
Black or African American	1		
Height Units: centimeters (cm) arithmetic mean standard deviation	-		
Weight Units: kilograms (kg) arithmetic mean standard deviation	-		

Body Surface Area (BSA)			
BSA = square root (height(cm) x weight (kg) / 3600.			
Units: meters squared (m^2)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)
Reporting group description: Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.	
Reporting group title	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)
Reporting group description: Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.	
Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
Reporting group description: Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m ² , tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.	

Primary: Combined Response Rate during the Induction Phase in Newly Diagnosed Multiple Myeloma (NDMM) Participants

End point title	Combined Response Rate during the Induction Phase in Newly Diagnosed Multiple Myeloma (NDMM) Participants ^{[1][2]}
End point description: Combined Response Rate is the percentage of participants with Complete Response (CR), including stringent Complete Response (sCR), and Very Good Partial Response (VGPR) according to the International Myeloma Working Group (IMWG) criteria during the Induction Phase (Cycles 1-13, 28-day cycles). CR=negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. Response Evaluable Population was defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment.	
End point type	Primary
End point timeframe: Day 1 of Cycles 1-13, 28-day cycles (Up to 1 year)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: percentage of participants				
number (confidence interval 95%)	27 (13 to 46)	24 (11 to 41)		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate (ORR) in Relapsed and/or Refractory Multiple Myeloma (RRMM) Participants

End point title	Overall Response Rate (ORR) in Relapsed and/or Refractory Multiple Myeloma (RRMM) Participants ^[3] ^[4]
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End point description:

ORR is the percentage of participants with CR, VGPR or PR according to IMWG criteria. CR=negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells (PC) in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. PR=50% reduction of serum M-protein and reduction in 24 hour urine M-protein by 90% or <200 mg/24 hour or decrease 50% difference between involved free light chain (FLC) levels or 50% reduction in bone marrow plasma cells if baseline percentage was 30%; and if present at Baseline, 50% reduction in the size of soft tissue plasmacytomas. Response Evaluable Population was defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment.

End point type	Primary
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End point timeframe:

Day 1 of each 28 day cycle (Up to 45 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	49 (37 to 61)			

Statistical analyses

Secondary: Number of Participants with Adverse Events (AEs), Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction and Serious Adverse Events (SAEs) in NDMM Participants

End point title	Number of Participants with Adverse Events (AEs), Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction and Serious Adverse Events (SAEs) in NDMM Participants ^[5]
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End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety Population was defined as all participants who receive at least 1 dose of any study drug.

End point type	Secondary
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End point timeframe:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: participants				
Any AE	35	34		
Grade 3 or Higher AEs	27	27		
AEs Resulting in Treatment Discontinuation	9	11		
AEs Resulting in Dose Reduction	11	10		
SAEs	17	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR + VGPR + PR (ORR), CR, VGPR, PR and Stable Disease (SD), Progressive Disease (PD) during the Induction Phase

End point title	Percentage of Participants with CR + VGPR + PR (ORR), CR, VGPR, PR and Stable Disease (SD), Progressive Disease (PD) during the Induction Phase ^[6]
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End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in

serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

End point type	Secondary
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End point timeframe:

Day 1 of Cycles 1-13, 28-day cycles (Up to 1 year)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: percentage of participants				
number (confidence interval 95%)				
CR + VGPR + PR	79 (61 to 91)	71 (53 to 85)		
CR	12 (3 to 28)	9 (2 to 24)		
VGPR	15 (5 to 32)	15 (5 to 31)		
PR	67 (48 to 82)	62 (44 to 78)		
SD	12 (3 to 28)	18 (7 to 35)		
PD	0 (0 to 0)	3 (1 to 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR + VGPR + PR (ORR), CR + VGPR, CR, VGPR, PR, SD and PD Throughout the Entire Treatment Period in NDMM Participants

End point title	Percentage of Participants with CR + VGPR + PR (ORR), CR + VGPR, CR, VGPR, PR, SD and PD Throughout the Entire Treatment Period in NDMM Participants ^[7]
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End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

End point type	Secondary
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End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: percentage of participants				
number (confidence interval 95%)				
CR + VGPR + PR	82 (65 to 93)	71 (53 to 85)		
CR + VGPR	36 (20 to 55)	32 (17 to 51)		
CR	15 (5 to 32)	12 (3 to 27)		
VGPR	21 (9 to 39)	21 (9 to 38)		
PR	67 (48 to 82)	59 (41 to 75)		
SD	18 (7 to 35)	18 (7 to 35)		
PD	0 (0 to 0)	6 (1 to 20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) in NDMM Participants during the Induction Phase

End point title	Time to Response (TTR) in NDMM Participants during the Induction Phase ^[8]
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End point description:

TTR is defined as the time interval from the date of the first dose of study treatment to the date of the first documented confirmed response of PR or better up to the initiation of alternative therapy in a participant who responded. Participants from the Response Evaluable Population, defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment, who responded.

End point type	Secondary
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End point timeframe:

Up to 1 year

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: months				
median (confidence interval 95%)	2.2 (0.95 to 2.92)	1.9 (0.95 to 1.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) in NDMM Participants

End point title	Duration of Response (DOR) in NDMM Participants ^[9]
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End point description:

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documented PD up to the initiation of alternative therapy. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, who responded. Responders without PD were censored at the date of SD or better prior to the date of alternative therapy. 99999 indicates 95% Confidence Interval (CI) Upper Limit was not estimable due to the low number of participants with events.

End point type	Secondary
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End point timeframe:

Up to 45 Months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: months				
median (confidence interval 95%)	32.2 (18.66 to 99999)	36.6 (19.75 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) in NDMM Participants

End point title	Time to Progression (TTP) in NDMM Participants ^[10]
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End point description:

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of disease progression. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: months				
median (confidence interval 95%)	30.9 (19.58 to 41.66)	32.2 (20.27 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in NDMM Participants

End point title	Progression Free Survival (PFS) in NDMM Participants ^[11]
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End point description:

PFS is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression or death. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD or death were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: months				
median (confidence interval 95%)	23.5 (15.67 to 39.59)	23.0 (15.90 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with AEs, SAEs, AEs Resulting in Discontinuation and AEs Resulting in Dose Reduction in NDMM Participants Remaining on Treatment after 13 Cycles

End point title	Number of Participants with AEs, SAEs, AEs Resulting in Discontinuation and AEs Resulting in Dose Reduction in NDMM Participants Remaining on Treatment after 13 Cycles ^[12]
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End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety Population was defined as all participants who receive at least 1 dose of any study drug. Number of participants analyzed is the number of participants who remained on treatment after 13 cycles.

End point type	Secondary
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End point timeframe:

First dose of study drug through 30 days after the last dose of drug (Up to 45 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	22		
Units: participants				
Any AE	22	20		
SAE	6	4		
AEs Resulting in Treatment Discontinuation	1	2		
AEs Resulting in Dose Reduction	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) during the Induction Phase in NDMM Participants

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) during the Induction Phase in NDMM Participants ^[13]
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End point description:

EORTC QLQ-C30 is a 30 item questionnaire that consists of 5 functional scales(physical, role, emotional,

cognitive, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patient evaluates their health status over previous week. 28 questions answered on a 4-point scale where: 1=Not at all (best) to 4=Very Much (worst), 2 questions answered on 7-point scale where 1=Very poor (worst) to 7=Excellent (best). All scales and single-item measures transformed to score: 0-100. For functioning scales and global QOL higher scores indicate better functioning (a positive change from Baseline indicates improvement); for symptom scales higher scores indicate more severe symptoms (a negative change from Baseline indicates improvement). Safety Population: participants who received at least 1 dose of any study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

Baseline (BL) (Day 1 of Cycle 1), Day 1 of Cycle 13 (Up to 1 year)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: score on a scale				
arithmetic mean (standard deviation)				
Global Health Status/QoL, Change from BL; Cycle 13	3.47 (± 30.783)	-5.43 (± 24.180)		
Physical functioning, Change from BL at Cycle 13	14.17 (± 35.675)	17.97 (± 20.640)		
Role functioning, Change from BL at Cycle 13	8.33 (± 43.127)	6.52 (± 35.441)		
Emotional functioning, Change from BL at Cycle 13	11.34 (± 27.837)	2.54 (± 15.977)		
Cognitive functioning, Change from BL at Cycle 13	2.78 (± 22.877)	-7.25 (± 14.058)		
Social functioning, Change from BL at Cycle 13	9.03 (± 39.921)	-11.59 (± 29.914)		
Fatigue, Change from BL at Cycle 13	-10.88 (± 35.307)	-6.76 (± 30.473)		
Nausea/Vomiting, Change from BL at Cycle 13	-4.86 (± 26.228)	-4.35 (± 19.603)		
Pain, Change from BL at Cycle 13	-13.89 (± 52.628)	-10.87 (± 39.443)		
Dyspnea, Change from BL at Cycle 13	-11.11 (± 37.644)	-7.25 (± 40.147)		
Insomnia, Change from BL at Cycle 13	-16.67 (± 46.104)	-10.14 (± 35.441)		
Appetite Loss, Change from BL at Cycle 13	-18.06 (± 42.822)	-7.25 (± 24.529)		
Constipation, Change from BL at Cycle 13	-13.89 (± 39.215)	-5.80 (± 41.013)		
Diarrhea, Change from BL at Cycle 13	-2.78 (± 30.954)	5.80 (± 19.207)		
Financial Difficulties, Change from BL at Cycle 13	4.17 (± 26.580)	1.45 (± 30.942)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR + VGR + PR (ORR), CR, VGPR, and PR in NDMM Participants Remaining on Treatment after 13 Cycles

End point title	Percentage of Participants with CR + VGR + PR (ORR), CR, VGPR, and PR in NDMM Participants Remaining on Treatment after 13 Cycles ^[14]
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End point description:

Percentage of participants with Overall Response (CR + VGPR + PR), CR, VGPR and PR according to IMWG criteria. CR=negative immunofixation of serum and urine; disappearance of soft tissue plasmacytomas; <5% PC in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. PR=50% reduction of serum M-protein and reduction in 24 hour urine M-protein by 90% or <200 mg/24 hour or decrease 50% difference between involved FLC levels or 50% reduction in bone marrow plasma cells if baseline percentage was 30%; and if present at Baseline, 50% reduction in the size of soft tissue plasmacytomas. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, with both an Induction and Maintenance response.

End point type	Secondary
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End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	21		
Units: percentage of participants				
number (not applicable)				
CR + VGPR + PR	75.0	85.7		
CR	16.7	19.0		
VGPR	20.8	28.6		
PR	37.5	38.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Ixazomib in NDMM Participants

End point title	Cmax: Maximum Observed Plasma Concentration for Ixazomib in NDMM Participants ^[15]
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End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary
End point timeframe:	
Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose	
Notes:	
[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: This endpoint is only applicable to the NDMM arms.	

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nanogram/mL (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=6,6)	64.283 (± 36.283)	46.600 (± 34.7722)		
Cycle 1 Day 15 (n=6,5)	53.145 (± 46.3782)	62.280 (± 39.4249)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to First Occurrence of Cmax for Ixazomib in NDMM Participants

End point title	Tmax: Time to First Occurrence of Cmax for Ixazomib in NDMM Participants ^[16]
End point description:	
PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.	
End point type	Secondary
End point timeframe:	
Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose	
Notes:	
[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.	
Justification: This endpoint is only applicable to the NDMM arms.	

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hour (hr)				
median (full range (min-max))				
Cycle 1 Day 1 (n=6,6)	1.250 (0.92 to 1.58)	1.040 (0.50 to 2.00)		

Cycle 1 Day 15 (n=6,5)	1.000 (0.45 to 4.00)	1.000 (0.50 to 1.50)		
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Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in NDMM Participants

End point title	AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in NDMM Participants ^[17]
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End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary
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End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the NDMM arms.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=6,5)	885.167 (± 354.1465)	792.600 (± 650.5665)		
Cycle 1 Day 15 (n=6,5)	1338.333 (± 746.2902)	1226.600 (± 527.5792)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with AEs, Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction, SAEs in RRMM Participants

End point title	Number of Participants with AEs, Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction, SAEs in RRMM Participants ^[18]
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End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical

product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety population was defined as all participants who received at least 1 dose of any study drug.

End point type	Secondary
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End point timeframe:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: participants				
Any AE	72			
Grade 3 or Higher AE	49			
AEs Resulting in Treatment Discontinuation	19			
AEs Resulting in Dose Reduction	30			
SAEs	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Ixazomib in RRMM Participants

End point title	Cmax: Maximum Observed Plasma Concentration for Ixazomib in RRMM Participants ^[19]
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End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary
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End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=6)	47.400 (± 36.7083)			
Cycle 1 Day 15 (n=7)	52.229 (± 39.6006)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to First Occurrence of Cmax for Ixazomib in RRMM Participants

End point title	Tmax: Time to First Occurrence of Cmax for Ixazomib in RRMM Participants ^[20]
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End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary
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End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168) hours postdose

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hr				
median (full range (min-max))				
Cycle 1 Day 1 (n=6)	1.225 (0.50 to 3.42)			
Cycle 1 Day 15 (n=7)	2.000 (0.50 to 8.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in RRMM Participants

End point title	AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in RRMM Participants ^[21]
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End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary
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End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=6)	518.167 (± 78.8274)			
Cycle 1 Day 15 (n=7)	1241.000 (± 657.4978)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with (CR + VGPR), CR, VGPR, PR, SD and PD in RRMM Participants

End point title	Percentage of Participants with (CR + VGPR), CR, VGPR, PR, SD and PD in RRMM Participants ^[22]
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End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

End point type	Secondary
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End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (confidence interval 95%)				
CR + VGPR	19 (11 to 30)			
CR	5 (2 to 13)			
VGPR	14 (7 to 24)			
PR	44 (32 to 56)			
SD	37 (26 to 49)			
PD	10 (4 to 19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) in RRMM Participants

End point title	Time to Response (TTR) in RRMM Participants ^[23]
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End point description:

TTR is defined as the time interval from the date of the first dose of study treatment to the date of the first documented confirmed response of PR or better up to the alternative therapy in a participant who responded. Participants from the Response Evaluable Population, defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment, who responded.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: months				
median (confidence interval 95%)	2.1 (0.95 to			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) in RRMM Participants

End point title	Duration of Response (DOR) in RRMM Participants ^[24]
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End point description:

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documented PD up to the alternative therapy. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, who responded. Responders without PD were censored at the date of SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: months				
median (confidence interval 95%)	26.3 (12.22 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) in RRMM Participants

End point title	Time to Progression (TTP) in RRMM Participants ^[25]
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End point description:

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of disease progression. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: months				
median (confidence interval 95%)	16.8 (11.30 to 24.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in RRMM Participants

End point title	Progression Free Survival (PFS) in RRMM Participants ^[26]
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End point description:

PFS is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression or death. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD or death were censored at the date of last response assessment that was SD or better prior to the date of the alternative therapy.

End point type	Secondary
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End point timeframe:

Up to 45 months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: months				
median (confidence interval 95%)	14.2 (9.69 to 20.57)			

Statistical analyses

Secondary: Change from Baseline in EORTC Quality of Life Questionnaire (QLQ-C30) in RRMM Participants

End point title	Change from Baseline in EORTC Quality of Life Questionnaire (QLQ-C30) in RRMM Participants ^[27]
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End point description:

EORTC QLQ-C30 is a 30 item questionnaire that consists of 5 functional scales (physical, role, emotional, cognitive, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patient evaluates their health status over previous week. 28 questions answered on 4-point scale where: 1=Not at all (best) to 4=Very Much (worst), 2 questions answered on 7-point scale where 1=Very poor (worst) to 7=Excellent (best). All scales and single-item measures transformed to score: 0-100. For functioning scales and global QOL higher scores indicate better functioning (a positive change from Baseline indicates improvement); for symptom scales higher scores indicate more severe symptoms (a negative change from Baseline indicates improvement). Safety Population: participants who received at least 1 dose of any study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

Baseline (Day 1 of Cycle 1), Day 1 of End of Treatment (EOT) (Up to 45 months)

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable to the RRMM arm.

End point values	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: score on a scale				
arithmetic mean (standard deviation)				
Global Health Status/QoL, Change from BL at EOT	-5.50 (± 20.798)			
Physical functioning, Change from BL at EOT	-6.00 (± 19.806)			
Role functioning, Change from BL at EOT	-7.67 (± 30.344)			
Emotional functioning, Change from BL at EOT	-5.00 (± 23.023)			
Cognitive functioning, Change from BL at EOT	-5.33 (± 19.760)			
Social functioning, Change from BL at EOT	-11.33 (± 26.177)			
Fatigue, Change from BL at EOT	5.11 (± 22.695)			
Nausea/Vomiting, Change from BL at EOT	3.33 (± 14.677)			
Pain, Change from BL at EOT	5.00 (± 28.621)			
Dyspnea, Change from BL at EOT	10.00 (± 27.970)			
Insomnia, Change from BL at EOT	-6.00 (± 27.512)			
Appetite Loss, Change from BL at EOT	4.67 (± 24.290)			

Constipation, Change from BL at EOT	2.00 (± 18.332)			
Diarrhea, Change from BL at EOT	6.00 (± 19.852)			
Financial Difficulties, Change from BL at EOT	4.00 (± 20.909)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)
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Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

Reporting group title	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)
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Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

Reporting group title	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
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Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m², tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.

Serious adverse events	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 36 (47.22%)	20 / 34 (58.82%)	30 / 78 (38.46%)
number of deaths (all causes)	3	2	5
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bladder cancer			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign bone neoplasm			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm benign			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema	Additional description: 1 TE death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM), 1 with Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM) and 1 with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM) and all 3 are not related.		
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM) and is not related.		
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
Light chain analysis increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 36 (8.33%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 7	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest	Additional description: One treatment-emergent (TE) death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM) and		

	is not related.		
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebral haemorrhage			
	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM) and is related.		
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Haemorrhage intracranial			
	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM) and is not related.		
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Syncope			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM) and is not related.		
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal ulcer			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM) and is not related.		
subjects affected / exposed	4 / 36 (11.11%)	2 / 34 (5.88%)	3 / 78 (3.85%)
occurrences causally related to treatment / all	1 / 4	0 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Localised infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis	Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM) and is related.		
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 400 mg/m ² + DEX 40 mg (NDMM)	Ixazomib 4.0 mg + CYC 300 mg/m ² + DEX 40 mg (RRMM)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 36 (94.44%)	34 / 34 (100.00%)	69 / 78 (88.46%)
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	7 / 34 (20.59%) 8	2 / 78 (2.56%) 2
Hypotension subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 34 (5.88%) 2	2 / 78 (2.56%) 2
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 10	7 / 34 (20.59%) 10	15 / 78 (19.23%) 22
Oedema peripheral subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 9	9 / 34 (26.47%) 11	5 / 78 (6.41%) 12
Pyrexia subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 6	6 / 34 (17.65%) 16	4 / 78 (5.13%) 5
Influenza like illness subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 34 (2.94%) 1	4 / 78 (5.13%) 5
Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 34 (2.94%) 1	4 / 78 (5.13%) 6
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4	4 / 34 (11.76%) 5	7 / 78 (8.97%) 7
Dyspnoea subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	6 / 78 (7.69%) 7
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	3 / 34 (8.82%) 3	10 / 78 (12.82%) 16
Anxiety subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 34 (5.88%) 2	0 / 78 (0.00%) 0
Confusional state			

subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 34 (5.88%) 3	1 / 78 (1.28%) 1
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	3 / 34 (8.82%) 3	1 / 78 (1.28%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	2 / 34 (5.88%) 4	0 / 78 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 34 (5.88%) 2	2 / 78 (2.56%) 2
Fall subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	2 / 34 (5.88%) 2	1 / 78 (1.28%) 1
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	3 / 34 (8.82%) 5	1 / 78 (1.28%) 1
Nervous system disorders			
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 7	10 / 34 (29.41%) 17	10 / 78 (12.82%) 17
Dizziness subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	2 / 34 (5.88%) 3	7 / 78 (8.97%) 9
Hypoaesthesia subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	3 / 34 (8.82%) 3	5 / 78 (6.41%) 6
Headache subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	3 / 34 (8.82%) 3	3 / 78 (3.85%) 4
Neuropathy peripheral subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 6	1 / 34 (2.94%) 1	3 / 78 (3.85%) 3

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 36 (30.56%)	11 / 34 (32.35%)	19 / 78 (24.36%)
occurrences (all)	16	19	32
Neutropenia			
subjects affected / exposed	6 / 36 (16.67%)	16 / 34 (47.06%)	15 / 78 (19.23%)
occurrences (all)	16	59	33
Thrombocytopenia			
subjects affected / exposed	4 / 36 (11.11%)	4 / 34 (11.76%)	18 / 78 (23.08%)
occurrences (all)	15	8	54
Leukopenia			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	4 / 78 (5.13%)
occurrences (all)	1	1	6
Lymphopenia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	4 / 78 (5.13%)
occurrences (all)	0	1	6
Iron deficiency anaemia			
subjects affected / exposed	2 / 36 (5.56%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences (all)	2	1	1
Eye disorders			
Cataract			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	5 / 78 (6.41%)
occurrences (all)	0	2	9
Glaucoma			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	0 / 78 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 36 (30.56%)	9 / 34 (26.47%)	26 / 78 (33.33%)
occurrences (all)	13	14	50
Nausea			
subjects affected / exposed	8 / 36 (22.22%)	10 / 34 (29.41%)	19 / 78 (24.36%)
occurrences (all)	16	12	34
Vomiting			
subjects affected / exposed	6 / 36 (16.67%)	9 / 34 (26.47%)	9 / 78 (11.54%)
occurrences (all)	13	11	16
Constipation			

subjects affected / exposed	8 / 36 (22.22%)	7 / 34 (20.59%)	8 / 78 (10.26%)
occurrences (all)	11	8	11
Dyspepsia			
subjects affected / exposed	1 / 36 (2.78%)	3 / 34 (8.82%)	6 / 78 (7.69%)
occurrences (all)	1	3	9
Abdominal pain upper			
subjects affected / exposed	2 / 36 (5.56%)	2 / 34 (5.88%)	4 / 78 (5.13%)
occurrences (all)	3	2	7
Flatulence			
subjects affected / exposed	0 / 36 (0.00%)	0 / 34 (0.00%)	4 / 78 (5.13%)
occurrences (all)	0	0	5
Gastritis			
subjects affected / exposed	2 / 36 (5.56%)	1 / 34 (2.94%)	1 / 78 (1.28%)
occurrences (all)	2	1	1
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	2 / 36 (5.56%)	2 / 34 (5.88%)	3 / 78 (3.85%)
occurrences (all)	3	2	5
Rash maculo-papular			
subjects affected / exposed	4 / 36 (11.11%)	0 / 34 (0.00%)	3 / 78 (3.85%)
occurrences (all)	6	0	4
Pruritus			
subjects affected / exposed	2 / 36 (5.56%)	1 / 34 (2.94%)	3 / 78 (3.85%)
occurrences (all)	2	1	5
Rash macular			
subjects affected / exposed	1 / 36 (2.78%)	2 / 34 (5.88%)	3 / 78 (3.85%)
occurrences (all)	1	2	6
Alopecia			
subjects affected / exposed	1 / 36 (2.78%)	3 / 34 (8.82%)	1 / 78 (1.28%)
occurrences (all)	1	3	1
Erythema			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences (all)	4	0	1
Erythema multiforme			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	1 / 78 (1.28%)
occurrences (all)	0	2	1

Rash pruritic subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3	0 / 34 (0.00%) 0	0 / 78 (0.00%) 0
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 2	3 / 34 (8.82%) 7	3 / 78 (3.85%) 4
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 7	6 / 34 (17.65%) 9	6 / 78 (7.69%) 9
Back pain subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	5 / 34 (14.71%) 6	7 / 78 (8.97%) 7
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 6	4 / 34 (11.76%) 6	2 / 78 (2.56%) 2
Bone pain subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	0 / 34 (0.00%) 0	6 / 78 (7.69%) 6
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 34 (2.94%) 1	4 / 78 (5.13%) 5
Pain in extremity subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 34 (2.94%) 1	4 / 78 (5.13%) 4
Osteoarthritis subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	1 / 34 (2.94%) 1	0 / 78 (0.00%) 0
Groin pain subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	0 / 78 (0.00%) 0
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 36 (25.00%) 10	3 / 34 (8.82%) 3	21 / 78 (26.92%) 42

Bronchitis			
subjects affected / exposed	5 / 36 (13.89%)	4 / 34 (11.76%)	12 / 78 (15.38%)
occurrences (all)	8	4	18
Nasopharyngitis			
subjects affected / exposed	5 / 36 (13.89%)	4 / 34 (11.76%)	6 / 78 (7.69%)
occurrences (all)	12	8	8
Respiratory tract infection			
subjects affected / exposed	3 / 36 (8.33%)	4 / 34 (11.76%)	8 / 78 (10.26%)
occurrences (all)	3	8	15
Herpes zoster			
subjects affected / exposed	6 / 36 (16.67%)	3 / 34 (8.82%)	5 / 78 (6.41%)
occurrences (all)	6	3	6
Influenza			
subjects affected / exposed	3 / 36 (8.33%)	0 / 34 (0.00%)	6 / 78 (7.69%)
occurrences (all)	3	0	6
Conjunctivitis			
subjects affected / exposed	2 / 36 (5.56%)	1 / 34 (2.94%)	5 / 78 (6.41%)
occurrences (all)	2	1	5
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)	3 / 34 (8.82%)	3 / 78 (3.85%)
occurrences (all)	2	3	3
Lower respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	5 / 78 (6.41%)
occurrences (all)	1	0	7
Pharyngitis			
subjects affected / exposed	2 / 36 (5.56%)	1 / 34 (2.94%)	3 / 78 (3.85%)
occurrences (all)	2	1	5
Pneumonia			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	4 / 78 (5.13%)
occurrences (all)	1	1	4
Oral herpes			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	3 / 78 (3.85%)
occurrences (all)	2	0	4
Cellulitis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	1 / 78 (1.28%)
occurrences (all)	2	0	1

Gastroenteritis subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 34 (5.88%) 2	1 / 78 (1.28%) 1
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 34 (5.88%) 2	0 / 78 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	4 / 34 (11.76%) 4	2 / 78 (2.56%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	3 / 34 (8.82%) 3	3 / 78 (3.85%) 3
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 34 (2.94%) 1	4 / 78 (5.13%) 9
Diabetes mellitus subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	1 / 34 (2.94%) 1	1 / 78 (1.28%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2014	Amendment 1: The protocol was amended to allow the enrollment of patients with relapsed and/or refractory multiple myeloma (RRMM) into the study. The evaluation of oral ixazomib when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) in this patient population. Study objectives and endpoints were added, and study procedures described for this patient population. The amendment also contained minor. Updates in study procedures to improve protocol clarity and compliance and align the study conduct with the sponsor's current guidelines and practices.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported