Clinical trial results:
A Phase 3, Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Summary

EudraCT number	2011-005468-10
Trial protocol	DE NL GB IT GR ES DK CZ
Global end of trial date	11 July 2022

Results information

Result version number	v1 (current)
This version publication date	26 July 2023
First version publication date	26 July 2023

Trial information

Trial identification

Sponsor protocol code	C16011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01659658
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to determine whether dexamethasone plus MLN9708 improves hematologic response and 2-year vital organ (that is, heart or kidney) deterioration and mortality rate versus a physician’s choice of a chemotherapy regimen.

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	12 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Korea, Republic of: 14
Worldwide total number of subjects	177
EEA total number of subjects	59

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)	84
From 65 to 84 years	93
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 66 investigative sites from 12 December 2012 to 11 July 2022. The study was prematurely terminated as it failed to meet the first primary endpoint at the first interim analysis.

Pre-assignment

Screening details:

Participants with a diagnosis of relapsed or refractory (R/R) systemic light chain amyloidosis (AL) were enrolled in the study to receive ixazomib capsules or physician's choice of therapy, which included dexamethasone tablets alone or in combination with either melphalan, cyclophosphamide, thalidomide or lenalidomide.

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	Arm A: Ixazomib + Dexamethasone

Arm description:

Participants received ixazomib 4 mg, capsules, orally, once on Days 1, 8, and 15 and dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle for up to a maximum of 95.2 months. Dexamethasone was increased up to 40 mg/day after 4 weeks, if tolerated.

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

Dosage and administration details:

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	Arm B: Dexamethasone + Melphalan

Arm description:

Participants received dexamethasone 20 mg, orally, and melphalan 0.22 mg/kg, orally once on Days 1 through 4 of each 28-day cycle, for up to a maximum of 72.4 months.

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

Dosage and administration details: Melphalan 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	
Arm title	Arm B: Dexamethasone + Cyclophosphamide

Arm description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22, and cyclophosphamide 500 mg, orally, on Days 1, 8, and 15 of each 28-day cycle for up to a maximum of 72.4 months.

Arm type	Active comparator
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	
Arm title	Arm B: Dexamethasone + Thalidomide

Arm description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle, and thalidomide daily at a starting dose of 50 mg and increased, as tolerated, to a maximum of 200 mg, orally for up to a maximum of 72.4 months.

Arm type	Active comparator
Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Thalidomide capsules	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Dexamethasone tablets	
Arm title	Arm B: Dexamethasone + Lenalidomide

Arm description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-

day cycle and lenalidomide 15 mg, orally, once on Days 1 through 21 every 28 days for up to a maximum of 72.4 months.

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

Dosage and administration details:

Lenalidomide capsules

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

Dosage and administration details:

Dexamethasone tablets

Number of subjects in period 1	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide
Started	90	26	10
Completed	0	0	0
Not completed	90	26	10
Lost to Follow-up	2	-	-
Withdrawal by Patient	18	4	2
Study Terminated by Sponsor	9	7	-
Reason not Specified	61	15	8

Number of subjects in period 1	Arm B: Dexamethasone + Thalidomide	Arm B: Dexamethasone + Lenalidomide
Started	2	49
Completed	0	0
Not completed	2	49
Lost to Follow-up	-	-
Withdrawal by Patient	-	11
Study Terminated by Sponsor	1	4
Reason not Specified	1	34

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Ixazomib + Dexamethasone
Reporting group description:	
Participants received ixazomib 4 mg, capsules, orally, once on Days 1, 8, and 15 and dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle for up to a maximum of 95.2 months. Dexamethasone was increased up to 40 mg/day after 4 weeks, if tolerated.	
Reporting group title	Arm B: Dexamethasone + Melphalan
Reporting group description:	
Participants received dexamethasone 20 mg, orally, and melphalan 0.22 mg/kg, orally once on Days 1 through 4 of each 28-day cycle, for up to a maximum of 72.4 months.	
Reporting group title	Arm B: Dexamethasone + Cyclophosphamide
Reporting group description:	
Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22, and cyclophosphamide 500 mg, orally, on Days 1, 8, and 15 of each 28-day cycle for up to a maximum of 72.4 months.	
Reporting group title	Arm B: Dexamethasone + Thalidomide
Reporting group description:	
Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle, and thalidomide daily at a starting dose of 50 mg and increased, as tolerated, to a maximum of 200 mg, orally for up to a maximum of 72.4 months.	
Reporting group title	Arm B: Dexamethasone + Lenalidomide
Reporting group description:	
Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle and lenalidomide 15 mg, orally, once on Days 1 through 21 every 28 days for up to a maximum of 72.4 months.	

Reporting group values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide
Number of subjects	90	26	10
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.4	64.8	60.0
standard deviation	± 9.83	± 8.73	± 14.97
Gender categorical Units: Subjects			
Female	35	11	4
Male	55	15	6
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	85	25	9
Unknown or Not Reported	5	0	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	16	9	5

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	70	17	5
More than one race	0	0	0
Unknown or Not Reported	3	0	0
Region of Enrollment			
Units: Subjects			
Canada	5	0	1
United States	24	2	3
Czechia	2	0	0
Denmark	0	0	0
France	3	1	0
Germany	8	5	0
United Kingdom	10	4	0
Greece	6	0	2
Italy	3	0	0
Netherlands	3	1	0
Spain	1	1	0
Turkey	1	0	0
Australia	8	0	0
Brazil	0	0	0
China	4	2	0
Israel	3	3	0
Japan	2	5	0
Korea, Republic of	7	2	4
Weight			
Units: kilograms (kg)			
arithmetic mean	77.33	70.95	70.20
standard deviation	± 16.740	± 12.476	± 21.815
Height			
Height was planned to be analysed for Intent-to-Treat (ITT) Population. Number of subjects analysed for this baseline characteristic is the number of participants with data available for height. Arm-wise number of subjects analysed is 90, 26, 10, 2, and 48.			
Units: centimeters (cm)			
arithmetic mean	170.40	167.07	170.65
standard deviation	± 10.507	± 8.662	± 13.274

Reporting group values	Arm B: Dexamethasone + Thalidomide	Arm B: Dexamethasone + Lenalidomide	Total
Number of subjects	2	49	177
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	65.0	64.9	
standard deviation	± 2.83	± 8.68	-
Gender categorical			
Units: Subjects			
Female	2	22	74
Male	0	27	103

Ethnicity Units: Subjects			
Hispanic or Latino	0	2	3
Not Hispanic or Latino	2	40	161
Unknown or Not Reported	0	7	13
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	32
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	1	48	141
More than one race	0	0	0
Unknown or Not Reported	0	0	3
Region of Enrollment Units: Subjects			
Canada	0	3	9
United States	0	13	42
Czechia	0	1	3
Denmark	1	2	3
France	0	1	5
Germany	0	3	16
United Kingdom	0	3	17
Greece	0	7	15
Italy	0	4	7
Netherlands	0	0	4
Spain	0	3	5
Turkey	0	0	1
Australia	0	6	14
Brazil	1	0	1
China	0	0	6
Israel	0	2	8
Japan	0	0	7
Korea, Republic of	0	1	14
Weight Units: kilograms (kg)			
arithmetic mean	50.10	75.35	
standard deviation	± 15.415	± 17.144	-
Height			
Height was planned to be analysed for Intent-to-Treat (ITT) Population. Number of subjects analysed for this baseline characteristic is the number of participants with data available for height. Arm-wise number of subjects analysed is 90, 26, 10, 2, and 48.			
Units: centimeters (cm)			
arithmetic mean	160.50	169.17	
standard deviation	± 13.435	± 10.532	-

End points

End points reporting groups

Reporting group title	Arm A: Ixazomib + Dexamethasone

Reporting group description:

Participants received ixazomib 4 mg, capsules, orally, once on Days 1, 8, and 15 and dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle for up to a maximum of 95.2 months. Dexamethasone was increased up to 40 mg/day after 4 weeks, if tolerated.

Reporting group title	Arm B: Dexamethasone + Melphalan

Reporting group description:

Participants received dexamethasone 20 mg, orally, and melphalan 0.22 mg/kg, orally once on Days 1 through 4 of each 28-day cycle, for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Cyclophosphamide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22, and cyclophosphamide 500 mg, orally, on Days 1, 8, and 15 of each 28-day cycle for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Thalidomide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle, and thalidomide daily at a starting dose of 50 mg and increased, as tolerated, to a maximum of 200 mg, orally for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Lenalidomide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle and lenalidomide 15 mg, orally, once on Days 1 through 21 every 28 days for up to a maximum of 72.4 months.

Subject analysis set title	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received dexamethasone 20 mg, orally, and melphalan 0.22 mg/kg, orally once on Days 1 through 4 of each 28-day cycle, for up to a maximum of 72.4 months OR dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22, and cyclophosphamide 500 mg, orally, on Days 1, 8, and 15 of each 28-day cycle for up to a maximum of 72.4 months OR dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle, and thalidomide daily at a starting dose of 50 mg and increased, as tolerated, to a maximum of 200 mg, orally for up to a maximum of 72.4 months OR dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle and lenalidomide 15 mg, orally, once on Days 1 through 21 every 28 days for up to a maximum of 72.4 months.

Primary: Percentage of Participants With Overall Hematologic Response

End point title	Percentage of Participants With Overall Hematologic Response

End point description:

Overall hematologic response was defined as the percentage of participants with complete response (CR), very good partial response (VGPR) and partial response (PR) based on central laboratory results and the 2010 International Society of Amyloidosis (ISA) Consensus Criteria as assessed by an adjudication committee. CR: Complete disappearance of M-protein from serum and urine on immunofixation, and normalisation of free light chain (FLC) ratio. VGPR: differential free light chain (difference between involved and uninvolved FLC levels; dFLC) < 40 mg/L. PR: ≥50% reduction in dFLC. Percentages were rounded off to the nearest decimal. ITT Population included all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	85	24	10	2
Units: percentage of participants				
number (confidence interval 95%)	53 (41.8 to 63.9)	58 (36.6 to 77.9)	30 (6.7 to 65.2)	50 (1.3 to 98.7)

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: percentage of participants				
number (confidence interval 95%)	51 (36.1 to 65.9)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Statistical analysis was planned to be collected and analyzed in a combined manner for the non-ixazomib arm groups versus ixazomib group in this outcome measure.	
Comparison groups	Arm A: Ixazomib + Dexamethasone v Arm B: Dexamethasone + Melphalan v Arm B: Dexamethasone + Thalidomide v Arm B: Dexamethasone + Cyclophosphamide v Arm B: Dexamethasone + Lenalidomide
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.7623 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.01

Notes:

[1] - Odds ratio was derived from a logistic regression model with treatment and 95% confidence interval (CI) for the odds ratio was based on the Wald approximation.

[2] - P-value was calculated from the unstratified Cochran-Mantel-Haenszel (CMH) test to compare hematologic response rate between the treatment arms.

Primary: 2-Year Vital Organ (Heart or Kidney) Deterioration and Mortality Rate

End point title	2-Year Vital Organ (Heart or Kidney) Deterioration and Mortality Rate[3]

End point description:

Cardiac (Heart) deterioration was defined as the need for hospitalisation for heart failure. Kidney deterioration was defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation. Vital organ deterioration was evaluated by an adjudication committee. Percentages were rounded off to the nearest decimal. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Up to 2 years

Notes:

[3] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	85	83		
Units: percentage of participants				
number (confidence interval 95%)	47 (36.1 to 58.2)	54 (41.7 to 64.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.351 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.38

Notes:

[4] - Odds ratio was derived from a logistic regression model with treatment and 95% CI for the odds ratio was based on the Wald approximation.
[5] - P-value was calculated from the unstratified CMH test to make comparisons between the 2 treatment arms.

Secondary: Percentage of Participants With Complete Hematologic Response

End point title	Percentage of Participants With Complete Hematologic Response[6]

End point description:

Complete hematologic response was defined as the percentage of participants with CR based on central laboratory results and the 2010 ISA Consensus Criteria as assessed by the investigator. CR: Complete disappearance of M-protein from serum and urine on immunofixation, and normalisation of FLC ratio. Percentages were rounded off to the nearest decimal. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: percentage of participants				
number (confidence interval 95%)	30 (20.8 to 40.6)	17 (10.0 to 26.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic Disease Progression Free Survival

End point title	Hematologic Disease Progression Free Survival

End point description:

Hematologic disease PFS was defined as the time from the date of randomisation to the date of first documentation of hematologic PD according to central laboratory results and ISA criteria as evaluated by an adjudication committee, or death due to any cause, whichever occurred first. As the study failed to meet the first primary endpoint per Sponsor’s specification at the first interim analysis, it was decided to terminate the study early without proceeding with the protocol-specified sequence of analyses. Owing to the same, data for this endpoint was not collected.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	0[9]	0[10]
Units: months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[7] - The data for this outcome measure was not collected due to study termination.

[8] - The data for this outcome measure was not collected due to study termination.

[9] - The data for this outcome measure was not collected due to study termination.

[10] - The data for this outcome measure was not collected due to study termination.

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: months				
median (full range (min-max))	(to)			

Notes:

[11] - The data for this outcome measure was not collected due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[12]

End point description:

PFS was defined as the time from the date of randomisation to the date of first documentation of hematologic disease progression, or organ (cardiac or renal) progression, or death due to any cause, whichever occurred first according to central laboratory results and ISA criteria as evaluated by the investigator. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (full range (min-max))	11.86 (0.8 to 72.0)	7.62 (0.0 to 71.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.135 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.09

Notes:

[13] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.

[14] - P-value was calculated using stratified log-rank test with stratification factors.

Secondary: Overall Survival

End point title	Overall Survival[15]

End point description:

Overall survival was defined as the time from the date of randomisation to the date of death. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (full range (min-max))	69.55 (0.8 to 95.5)	43.17 (0.0 to 82.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.389 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.29

Notes:

[16] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.
[17] - P-value was calculated using log-rank test stratified by the stratification factors.

Secondary: Time to Vital Organ (Heart or Kidney) Deterioration and Mortality Rate

End point title	Time to Vital Organ (Heart or Kidney) Deterioration and Mortality Rate[18]

End point description:

Time to vital organ deterioration or death was assessed by the investigator and defined as the time from randomisation to vital organ (heart or kidney) deterioration or death, whichever occurs first. Cardiac deterioration is defined as the need for hospitalisation for heart failure. Kidney deterioration is defined as progression to ESRD with the need for maintenance dialysis or renal transplantation. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From randomisation to time of vital organ deterioration or death (up to 115 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (full range (min-max))	38.67 (0.0 to 70.5)	26.09 (0.0 to 71.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.036 [20]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.97

Notes:

[19] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.
[20] - P-value was calculated using log-rank test stratified by the stratification factors.

Secondary: Percentage of Participants With Best Vital Organ (Cardiac and/or Kidney) Response

End point title	Percentage of Participants With Best Vital Organ (Cardiac and/or Kidney) Response[21]

End point description:

Vital organ (heart and kidney) response rate was defined as the percentage of participants who achieved vital organ response according to central laboratory results and ISA criteria as evaluated by an adjudication committee. A vital organ response was defined as response of 1 or 2 of the involved vital organs with no change from Baseline in the rest of involved vital organs. Percentages were rounded off to the nearest decimal. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	85	83		
Units: percentage of participants				
number (confidence interval 95%)	19 (11.2 to 28.8)	12 (5.9 to 21.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.226 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	3.99

Notes:

[22] - Odds ratio was calculated from a logistic regression model with treatment and 95% CI for the odds ratio was based on the Wald approximation.
[23] - P-value was calculated from the unstratified CMH test to compare vital organ response rate between the 2 treatment arms.

Secondary: Vital Organ Progression Free Survival

End point title	Vital Organ Progression Free Survival[24]

End point description:

Vital organ PFS is defined as the time from the date of randomisation to the date of first documentation of progression of vital organ (heart or kidney) according to central laboratory results and ISA criteria as evaluated by an adjudication committee, or death due to any cause, whichever occurs first. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (full range (min-max))	15.77 (0.0 to 72.0)	11.01 (0.0 to 71.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.163 [26]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.12

Notes:

[25] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.

[26] - P-value was calculated using stratified log-rank test with stratification factors.

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

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

End point description:

A SAE is defined as any untoward medical occurrence that at any dose which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or medically important event. Safety Population included all participants who received at least 1 dose of any treatment drug.

End point type	Secondary

End point timeframe:

From first dose of study drug through 30 days after administration of the last dose of study drug (up to 115 months)

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	26	10	1
Units: participants	44	11	2	0

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hematologic Response

End point title	Duration of Hematologic Response[27]

End point description:

Duration of hematologic response (DOR) was defined as the time from the date of first documentation of a hematologic response to the date of first documented hematologic disease progression as determined by the investigator. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised. Number of subjects analysed is the number of hematologic responders. 9.999=Median was not estimable due to excess amount of censoring among the participants for the analysis.

End point type	Secondary

End point timeframe:

From time of first documented response to disease progression (up to 115 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49	45		
Units: months				
median (full range (min-max))	9.999 (1.8 to 71.1)	21.19 (0.0 to 69.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Subsequent Anticancer Treatment

End point title	Time To Subsequent Anticancer Treatment[28]

End point description:

Time to subsequent anticancer therapy was defined as the time from randomisation to the first date of subsequent anticancer therapy. Participants without subsequent anticancer therapy were censored at the date of death or last known to be alive. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until subsequent anticancer treatment (up to 115 months)

Notes:

[28] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (full range (min-max))	26.48 (0.8 to 95.5)	12.45 (0.0 to 72.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.01 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.88

Notes:

[29] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.
[30] - P-value was calculated using stratified log-rank test with stratification factors.

Secondary: Time To Treatment Failure (TTF)

End point title	Time To Treatment Failure (TTF)[31]

End point description:

TTF was defined as the time from randomisation to the date of first documented treatment failure. Treatment failure was defined as: 1) death due to any cause; 2) hematologic progression or major organ progression according to central laboratory results and ISA criteria as evaluated by the investigator; 3) clinically morbid organ disease requiring additional therapy; or 4) withdrawn for any reason. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised.

End point type	Secondary

End point timeframe:

From first dose of study drug until discontinuation of study drug due to disease progression or unacceptable toxicity, or death whichever occurs first (up to 115 months)

Notes:

[31] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	90	87		
Units: months				
median (confidence interval 95%)	10.32 (7.52 to 14.82)	5.32 (4.14 to 7.82)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm A: Ixazomib + Dexamethasone v ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.025 [33]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.96

Notes:

[32] - Unadjusted stratified Cox regression model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors.
[33] - P-value was calculated using stratified log-rank test with stratification factors.

Secondary: Change From Baseline in Amyloidosis Symptom Scale Score

End point title	Change From Baseline in Amyloidosis Symptom Scale Score

End point description:

The amyloidosis symptom scale questionnaire is a participant completed questionnaire that evaluates symptom severity of 3 symptoms: Swelling, Shortness of Breath and Dizziness, each rated on an 11-point scale where: 0=no symptoms to 10=very severe symptoms. Higher scores indicate worsening of symptoms. As the study failed to meet the first primary endpoint per Sponsor's specification at the first interim analysis, it was decided to terminate the study early without proceeding with the protocol-specified sequence of analyses. Owing to the same, data for this endpoint was not collected.

End point type	Secondary

End point timeframe:

At screening (Baseline); Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Day 1 of every 3 cycles until disease progression (up to 115 months) [cycle length=28 days]

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[34]	0[35]	0[36]	0[37]
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[34] - The data for this outcome measure was not collected due to study termination.
[35] - The data for this outcome measure was not collected due to study termination.
[36] - The data for this outcome measure was not collected due to study termination.
[37] - The data for this outcome measure was not collected due to study termination.

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	0[38]			
Units: score on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[38] - The data for this outcome measure was not collected due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 36-item Short Form General Health Survey (SF-36) General Health Survey Score

End point title	Change From Baseline in 36-item Short Form General Health Survey (SF-36) General Health Survey Score

End point description:

SF-36 Version 2 is a multipurpose, participant completed, short-form health survey with 36 questions that consists of an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. Physical component summary(PCS) is mostly contributed by physical function(PF), role physical(RP), bodily pain(BP), and general health(GH). Mental component summary(MCS) is mostly contributed by mental health(MH), role emotional(RE), social function(SF), and vitality(VT). Each component on the on the SF-36 item health survey is scored from 0(best) to 100(worst). As the study failed to meet the first primary endpoint per Sponsor's specification at the first interim analysis, it was decided to terminate the study early without proceeding with the protocol-specified sequence of analyses. Owing to the same, data for this endpoint was not collected.

End point type	Secondary

End point timeframe:

At screening (Baseline); Cycle 1, Day 1; Cycle 3, Day 1; Day 1 of every 3 cycles until disease progression (up to 115 months) [cycle length=28 days]

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[39]	0[40]	0[41]	0[42]
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[39] - The data for this outcome measure was not collected due to study termination.

[40] - The data for this outcome measure was not collected due to study termination.

[41] - The data for this outcome measure was not collected due to study termination.

[42] - The data for this outcome measure was not collected due to study termination.

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	0[43]			
Units: score on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[43] - The data for this outcome measure was not collected due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Score

End point title	Change From Baseline in Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Score

End point description:

The FACT/GOG-Ntx is a participant completed questionnaire that comprises 11 individual items evaluating symptoms of neurotoxicity on a 5-point scale where: 0=not at all (best) to 4=very much for a total possible score of 0 to 44. As the study failed to meet the first primary endpoint per Sponsor's specification at the first interim analysis, it was decided to terminate the study early without proceeding with the protocol-specified sequence of analyses. Owing to the same, data for this endpoint was not collected.

End point type	Secondary

End point timeframe:

At screening (Baseline); Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Day 1 of every 3 cycles until disease progression (up to 115 months) [cycle length=28 days]

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[44]	0[45]	0[46]	0[47]
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[44] - The data for this outcome measure was not collected due to study termination.

[45] - The data for this outcome measure was not collected due to study termination.

[46] - The data for this outcome measure was not collected due to study termination.

[47] - The data for this outcome measure was not collected due to study termination.

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	0[48]			
Units: score on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[48] - The data for this outcome measure was not collected due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Ixazomib

End point title	Plasma Concentration of Ixazomib[49]

End point description:

As prespecified in the protocol, data for this outcome measure was planned to be collected for ixazomib arm group only. Pharmacokinetic (PK) Analysis Population included participants with at least one PK sample that was collected and analysed. Number analysed (n) is the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: 1, 4 hours postdose, Day 14: 144 hours postdose; Cycle 2, Day 1: predose, Day 14: 144 hours postdose; Cycles 3 to 10, Day 1: predose (cycle length=28 days)

Notes:

[49] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: 1 Hour Post-dose(n=77)	16.518 (± 97.0462)			
Cycle 1 Day 14: 4 Hours Post-dose(n=78)	10.652 (± 121.7231)			
Cycle 1 Day 14: 144 Hours Post-dose(n=73)	3.875 (± 100.3055)			
Cycle 2 Day 1: Pre-dose(n=70)	2.000 (± 59.4061)			
Cycle 2 Day 14: 144 Hours Post-dose(n=60)	4.726 (± 115.5653)			
Cycle 3 Day 1: Pre-dose(n=65)	2.187 (± 59.1378)			
Cycle 4 Day 1 Pre-dose(n=59)	2.276 (± 59.3690)			
Cycle 5 Day 1 Pre-dose(n=56)	2.264 (± 54.8881)			
Cycle 6 Day 1: Pre-dose(n=54)	2.235 (± 60.4723)			
Cycle 7 Day 1: Pre-dose(n=45)	2.299 (± 53.7147)			
Cycle 8 Day 1: Pre-dose(n=43)	2.038 (± 58.6811)			
Cycle 9 Day 1: Pre-dose(n=42)	2.143 (± 55.0715)			
Cycle 10 Day 1: Pre-dose(n=42)	2.232 (± 57.4067)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in Each Category of the EuroQol 5-Dimensional (EQ-5D) Questionnaire Score

End point title	Number of Participants in Each Category of the EuroQol 5-Dimensional (EQ-5D) Questionnaire Score[50]

End point description:

The European Quality of Life (EuroQOL) 5-Dimensional (EQ-5D) is a patient completed questionnaire consisting of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The

descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 3 possible choices: no problems to extreme problems. Higher scores=worsening of the quality of life. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses. UA=Usual Activities.

End point type	Secondary

End point timeframe:

At Week 28 of the OS follow-up

Notes:

[50] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[51]	1		
Units: participants				
Mobility: No Problems in Walking About		0		
Mobility: Some Problem in Walking About		1		
Mobility: Confined to Bed		0		
Self-Care: No Problems With Self- Care		0		
Self-Care: Some Problems Washing or Dressing		1		
Self-Care: Unable to Wash or Dress		0		
Usual Activities: No Problems With Performing UA		0		
Usual Activities: Some Problem With Performing UA		1		
Usual Activities: Unable to Performing UA		0		
Pain/Discomfort: No Pain or Discomfort		0		
Pain/Discomfort: Moderate Pain or Discomfort		1		
Pain/Discomfort: Extreme Pain or Discomfort		0		
Anxiety/Depression: Not Anxious or Depressed		0		
Anxiety/Depression: Moderately Anxious or Depresse		0		
Anxiety/Depression: Extremely Anxious or Depressed		1		

Notes:

[51] - No participants were available for analysis in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Medical Encounters Participants Experience

End point title	Number of Medical Encounters Participants Experience

End point description:

Medical encounters were planned to be recorded as the number of admissions to an inpatient and outpatient setting for any reason (including length of stay, inpatient, outpatient and reason), number of missing days from work or other activities by participant or care-giver. As the study failed to meet the first primary endpoint per Sponsor's specification at the first interim analysis, it was decided to terminate the study early without proceeding with the protocol-specified sequence of analyses. Owing to the same, data for this endpoint was not collected.

End point type	Secondary

End point timeframe:

At screening; Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; Day 1 of every 3 cycles until disease progression (up to 115 months) [cycle length=28 days]

End point values	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Thalidomide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[52]	0[53]	0[54]	0[55]
Units: participants				

Notes:

[52] - The data for this outcome measure was not collected due to study termination.

[53] - The data for this outcome measure was not collected due to study termination.

[54] - The data for this outcome measure was not collected due to study termination.

[55] - The data for this outcome measure was not collected due to study termination.

End point values	Arm B: Dexamethasone + Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	0[56]			
Units: participants				

Notes:

[56] - The data for this outcome measure was not collected due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol 5-Dimension 3-Level (EQ-5D-3L) Visual Analogue Scale Score

End point title	EuroQol 5-Dimension 3-Level (EQ-5D-3L) Visual Analogue Scale Score[57]

End point description:

The EQ visual analogue scale (VAS) records the participant's self-rated health on a 20 centimeter vertical VAS that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Baseline is defined as the value collected at the time closest to, but prior to, the start of study drug administration. As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this outcome measure. ITT Population included all participants who were randomised. Number of subjects analysed is the number of participants with data available for analyses. 99999=Standard Deviation (SD) was not estimable for 1 participant.

End point type	Secondary

End point timeframe:

At Week 28 of the OS follow-up

Notes:

[57] - 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: As prespecified in the protocol, data was planned to be collected and analysed in a combined way for non-ixazomib arm groups in this endpoint.

End point values	Arm A: Ixazomib + Dexamethasone	ArmB:Dex + Melphalan/Cyclophosphamide/Thalidomide/Lenalidomide		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[58]	1		
Units: score on a scale				
arithmetic mean (standard deviation)	()	23.0 (± 99999)		

Notes:

[58] - No participants were available for analysis in this arm.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through 30 days after administration of the last dose of study drug (up to 115 months)

Adverse event reporting additional description:

All-cause mortality: ITT Population included all participants who were randomized. Serious and other adverse events: Safety Population included all participants who received at least 1 dose of any treatment drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Arm A: Ixazomib + Dexamethasone

Reporting group description:

Participants received ixazomib 4 mg, capsules, orally, once on Days 1, 8, and 15 and dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle for up to a maximum of 95.2 months. Dexamethasone was increased up to 40 mg/day after 4 weeks, if tolerated.

Reporting group title	Arm B: Dexamethasone + Cyclophosphamide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22, and cyclophosphamide 500 mg, orally, on Days 1, 8, and 15 of each 28-day cycle for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Lenalidomide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle and lenalidomide 15 mg, orally, once on Days 1 through 21 every 28 days for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Melphalan

Reporting group description:

Participants received dexamethasone 20 mg, orally, and melphalan 0.22 mg/kg, orally once on Days 1 through 4 of each 28-day cycle, for up to a maximum of 72.4 months.

Reporting group title	Arm B: Dexamethasone + Thalidomide

Reporting group description:

Participants received dexamethasone 20 mg, orally, once weekly on Days 1, 8, 15, and 22 of each 28-day cycle, and thalidomide daily at a starting dose of 50 mg and increased, as tolerated, to a maximum of 200 mg, orally for up to a maximum of 72.4 months.

Serious adverse events	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Lenalidomide
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 90 (48.89%)	2 / 10 (20.00%)	17 / 47 (36.17%)
number of deaths (all causes)	40	4	22
number of deaths resulting from adverse events	6	1	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal adenoma			

subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Prostate cancer			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Peripheral artery thrombosis			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Asthenia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Sudden cardiac death			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Oedema peripheral			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Pleural effusion			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Hypoxia			

subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	4 / 90 (4.44%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Pulmonary embolism			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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

Femoral neck fracture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Craniocerebral injury			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Accidental overdose			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Skin laceration			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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 amyloidosis			

subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bradycardia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Ventricular arrhythmia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Cardiac failure congestive			
subjects affected / exposed	3 / 90 (3.33%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery dissection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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 arrest			
subjects affected / exposed	3 / 90 (3.33%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	4 / 90 (4.44%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 4	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Post herpetic neuralgia			

subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Spinal cord infarction			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Gastric ulcer			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Diarrhoea			

subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Constipation			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Subileus			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Rash maculo-papular			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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			
Renal impairment			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 90 (2.22%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	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	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Jaw cyst			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Muscular weakness			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Cellulitis			
subjects affected / exposed	4 / 90 (4.44%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Bronchitis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster cutaneous disseminated			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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

Influenza			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	1 / 5	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Pneumonia fungal			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Metabolism and nutrition disorders			
Steroid diabetes			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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
Dehydration			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (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

Serious adverse events	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Thalidomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 26 (42.31%)	0 / 1 (0.00%)	
number of deaths (all causes)	14	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal adenoma			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery dissection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Post herpetic neuralgia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infarction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw cyst			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster cutaneous disseminated			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 26 (15.38%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Steroid diabetes			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: Ixazomib + Dexamethasone	Arm B: Dexamethasone + Cyclophosphamide	Arm B: Dexamethasone + Lenalidomide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 90 (95.56%)	9 / 10 (90.00%)	46 / 47 (97.87%)
Vascular disorders			
Hypotension			

subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	4 / 47 (8.51%)
occurrences (all)	3	1	5
Hypertension			
subjects affected / exposed	11 / 90 (12.22%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	15	0	1
Deep vein thrombosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
Orthostatic hypotension			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	8	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 90 (7.78%)	0 / 10 (0.00%)	7 / 47 (14.89%)
occurrences (all)	14	0	11
Peripheral swelling			
subjects affected / exposed	5 / 90 (5.56%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	6	1	2
Oedema peripheral			
subjects affected / exposed	41 / 90 (45.56%)	3 / 10 (30.00%)	17 / 47 (36.17%)
occurrences (all)	66	8	29
Non-cardiac chest pain			
subjects affected / exposed	2 / 90 (2.22%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Malaise			
subjects affected / exposed	2 / 90 (2.22%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	2	1	0
Influenza like illness			
subjects affected / exposed	8 / 90 (8.89%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	9	0	1
Fatigue			
subjects affected / exposed	40 / 90 (44.44%)	3 / 10 (30.00%)	24 / 47 (51.06%)
occurrences (all)	62	4	47
Chills			

subjects affected / exposed	1 / 90 (1.11%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	1	1	2
Asthenia			
subjects affected / exposed	8 / 90 (8.89%)	0 / 10 (0.00%)	6 / 47 (12.77%)
occurrences (all)	11	0	7
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	5	0	3
Haemoptysis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
Epistaxis			
subjects affected / exposed	10 / 90 (11.11%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	13	1	2
Dyspnoea			
subjects affected / exposed	19 / 90 (21.11%)	0 / 10 (0.00%)	12 / 47 (25.53%)
occurrences (all)	34	0	14
Cough			
subjects affected / exposed	13 / 90 (14.44%)	2 / 10 (20.00%)	4 / 47 (8.51%)
occurrences (all)	17	2	5
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 90 (2.22%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 90 (4.44%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	4	1	1
Anxiety			
subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Nightmare			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Mood swings			

subjects affected / exposed	1 / 90 (1.11%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
Mood altered			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences (all)	5	0	2
Irritability			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	32 / 90 (35.56%)	2 / 10 (20.00%)	8 / 47 (17.02%)
occurrences (all)	39	2	8
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	6 / 47 (12.77%)
occurrences (all)	5	0	7
Platelet count decreased			
subjects affected / exposed	4 / 90 (4.44%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	5	0	0
Weight decreased			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	1	0	4
Weight increased			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	6	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	7	0	3
Fall			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences (all)	9	0	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	8	0	1
Sinus tachycardia			

subjects affected / exposed	4 / 90 (4.44%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Palpitations			
subjects affected / exposed	5 / 90 (5.56%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	6	1	2
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Dizziness			
subjects affected / exposed	14 / 90 (15.56%)	1 / 10 (10.00%)	7 / 47 (14.89%)
occurrences (all)	17	1	8
Disturbance in attention			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	0	1	2
Dysaesthesia			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	7	0	0
Headache			
subjects affected / exposed	10 / 90 (11.11%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	14	0	5
Paraesthesia			
subjects affected / exposed	7 / 90 (7.78%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	10	0	4
Peripheral sensory neuropathy			
subjects affected / exposed	20 / 90 (22.22%)	0 / 10 (0.00%)	10 / 47 (21.28%)
occurrences (all)	22	0	18
Syncope			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	4	0	4
Taste disorder			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	3
Dysgeusia			
subjects affected / exposed	6 / 90 (6.67%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	8	1	0

Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	5 / 90 (5.56%)	1 / 10 (10.00%)	3 / 47 (6.38%)
occurrences (all)	6	3	6
Neutropenia			
subjects affected / exposed	0 / 90 (0.00%)	2 / 10 (20.00%)	4 / 47 (8.51%)
occurrences (all)	0	2	6
Anaemia			
subjects affected / exposed	7 / 90 (7.78%)	2 / 10 (20.00%)	9 / 47 (19.15%)
occurrences (all)	11	3	15
Leukopenia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 90 (4.44%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	4	0	1
Eye disorders			
Cataract			
subjects affected / exposed	7 / 90 (7.78%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	9	0	1
Vision blurred			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	5	0	0
Lacrimation increased			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	5	0	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	3
Myopia			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	32 / 90 (35.56%)	1 / 10 (10.00%)	22 / 47 (46.81%)
occurrences (all)	66	1	34

Dyspepsia			
subjects affected / exposed	7 / 90 (7.78%)	1 / 10 (10.00%)	3 / 47 (6.38%)
occurrences (all)	10	1	3
Flatulence			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	5	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Constipation			
subjects affected / exposed	18 / 90 (20.00%)	4 / 10 (40.00%)	13 / 47 (27.66%)
occurrences (all)	30	4	22
Anal haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	7 / 90 (7.78%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	7	1	1
Abdominal pain			
subjects affected / exposed	9 / 90 (10.00%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	13	1	0
Abdominal distension			
subjects affected / exposed	10 / 90 (11.11%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences (all)	12	0	2
Haemorrhoids			
subjects affected / exposed	2 / 90 (2.22%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	23 / 90 (25.56%)	3 / 10 (30.00%)	5 / 47 (10.64%)
occurrences (all)	35	3	6
Mouth ulceration			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	13 / 90 (14.44%)	2 / 10 (20.00%)	6 / 47 (12.77%)
occurrences (all)	35	2	8
Tongue haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	7 / 90 (7.78%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	7	0	1
Dry skin			
subjects affected / exposed	4 / 90 (4.44%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	5	0	1
Erythema			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	7	0	0
Rash maculo-papular			
subjects affected / exposed	12 / 90 (13.33%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	13	2	7
Rash macular			
subjects affected / exposed	3 / 90 (3.33%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	4	0	4
Pruritus			
subjects affected / exposed	5 / 90 (5.56%)	2 / 10 (20.00%)	4 / 47 (8.51%)
occurrences (all)	6	2	4
Night sweats			
subjects affected / exposed	1 / 90 (1.11%)	2 / 10 (20.00%)	2 / 47 (4.26%)
occurrences (all)	1	2	2
Rash pruritic			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	7	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 90 (0.00%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			

subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	3	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 90 (12.22%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	19	1	5
Back pain			
subjects affected / exposed	15 / 90 (16.67%)	1 / 10 (10.00%)	5 / 47 (10.64%)
occurrences (all)	19	1	6
Intervertebral disc protrusion			
subjects affected / exposed	0 / 90 (0.00%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	9 / 90 (10.00%)	0 / 10 (0.00%)	7 / 47 (14.89%)
occurrences (all)	10	0	9
Muscular weakness			
subjects affected / exposed	12 / 90 (13.33%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	13	0	6
Pain in extremity			
subjects affected / exposed	10 / 90 (11.11%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	12	0	2
Myalgia			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	6	0	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 90 (8.89%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	9	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 90 (2.22%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	2	0	3
Urinary tract infection			
subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	4 / 47 (8.51%)
occurrences (all)	5	1	8
Upper respiratory tract infection			

subjects affected / exposed	22 / 90 (24.44%)	1 / 10 (10.00%)	10 / 47 (21.28%)
occurrences (all)	31	1	19
Tooth abscess			
subjects affected / exposed	1 / 90 (1.11%)	1 / 10 (10.00%)	0 / 47 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection			
subjects affected / exposed	3 / 90 (3.33%)	1 / 10 (10.00%)	1 / 47 (2.13%)
occurrences (all)	7	1	1
Nasopharyngitis			
subjects affected / exposed	8 / 90 (8.89%)	4 / 10 (40.00%)	3 / 47 (6.38%)
occurrences (all)	15	6	3
Lower respiratory tract infection			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	8	0	5
Influenza			
subjects affected / exposed	7 / 90 (7.78%)	1 / 10 (10.00%)	3 / 47 (6.38%)
occurrences (all)	8	1	3
Herpes zoster			
subjects affected / exposed	8 / 90 (8.89%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	8	0	3
Conjunctivitis			
subjects affected / exposed	6 / 90 (6.67%)	0 / 10 (0.00%)	1 / 47 (2.13%)
occurrences (all)	6	0	1
Pneumonia			
subjects affected / exposed	3 / 90 (3.33%)	0 / 10 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 90 (12.22%)	2 / 10 (20.00%)	4 / 47 (8.51%)
occurrences (all)	14	2	4
Fluid retention			
subjects affected / exposed	1 / 90 (1.11%)	0 / 10 (0.00%)	3 / 47 (6.38%)
occurrences (all)	1	0	3
Hyperglycaemia			
subjects affected / exposed	3 / 90 (3.33%)	0 / 10 (0.00%)	4 / 47 (8.51%)
occurrences (all)	3	0	4

Hypokalaemia			
subjects affected / exposed	5 / 90 (5.56%)	1 / 10 (10.00%)	2 / 47 (4.26%)
occurrences (all)	5	1	3
Iron deficiency			
subjects affected / exposed	5 / 90 (5.56%)	0 / 10 (0.00%)	2 / 47 (4.26%)
occurrences (all)	5	0	2

Non-serious adverse events	Arm B: Dexamethasone + Melphalan	Arm B: Dexamethasone + Thalidomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 26 (92.31%)	1 / 1 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	7 / 26 (26.92%)	0 / 1 (0.00%)	
occurrences (all)	8	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	4	0	

Malaise			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	7 / 26 (26.92%)	1 / 1 (100.00%)	
occurrences (all)	10	2	
Chills			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Haemoptysis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	3 / 26 (11.54%)	1 / 1 (100.00%)	
occurrences (all)	5	3	
Cough			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nightmare			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Mood swings			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Mood altered			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	3 / 26 (11.54%)	1 / 1 (100.00%)	
occurrences (all)	4	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Weight decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Disturbance in attention			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dysaesthesia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 26 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	4	
Syncope			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Taste disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Anaemia			
subjects affected / exposed	4 / 26 (15.38%)	0 / 1 (0.00%)	
occurrences (all)	7	0	
Leukopenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Lacrimation increased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Myopia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 26 (15.38%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	3 / 26 (11.54%)	1 / 1 (100.00%)	
occurrences (all)	3	2	
Anal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	4	0	

Haemorrhoids			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 26 (15.38%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Mouth ulceration			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Tongue haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	1 / 26 (3.85%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Pruritus			

subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash pruritic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 26 (7.69%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	1 / 26 (3.85%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Muscular weakness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Myalgia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Tooth abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 26 (3.85%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 26 (11.54%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Fluid retention			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Iron deficiency			
subjects affected / exposed	0 / 26 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2020	Following updates were made as per Amendment 6: -Added primary study results from the first interim analysis (IA)-Defined the ongoing safety assessments. -Discontinued all disease and efficacy response assessments, including central laboratory assessments of efficacy and safety, for protocol purposes. -Discontinued pharmacokinetic (PK) sampling, health utilisation assessments and collection of concomitant medications and procedures for ongoing participants. -Specified that no further adjudication committee (AC) reviews were needed. -Updated the number of participants in the study and the estimated study duration. -Discontinued the PFS and OS follow-up periods. -Defined overdose. -Removed mention of the Safety Management Attachment (SMA). -Updated the procedures for SAE reporting. -Specified that no further independent data monitoring committee reviews of safety and efficacy were needed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 July 2022	The study was terminated based on Sponsor’s decision as it failed to meet the first primary endpoint at the first interim analysis.	-

Notes:

Limitations and caveats

None reported