



Clinical trial results:

A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)

Summary

EudraCT number	2017-003977-32
Trial protocol	CZ GR NL PL
Global end of trial date	26 June 2023

Results information

Result version number	v1 (current)
This version publication date	23 June 2024
First version publication date	23 June 2024

Trial information

Trial identification

Sponsor protocol code	C16047
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03439293
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	26 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study is to evaluate the proportion of participants with a response of very good partial response (VGPR) or better to IDd treatment.

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	13 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	61
EEA total number of subjects	49

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)	19

From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at investigative sites in Greece, the Czech Republic, the United States, Poland, France and the Netherlands from 13 March 2018 to 26 June 2023.

Pre-assignment

Screening details:

Participants with a diagnosis of relapsed and/or refractory multiple myeloma (RRMM) took part in the study to receive ixazomib + daratumumab + dexamethasone.

Period 1

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

Arms

Arm title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
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Arm description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

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

Dosage and administration details:

Ixazomib was administered at 4 mg orally for the first 3 weeks of each 28-day cycle (Days 1, 8, and 15).

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab was administered IV at 16 mg/kg every week for Cycles 1 and 2 (on Days 1, 8, 15, and 22), every other week in Cycles 3 to 6 (on Days 1 and 15), and every 4 weeks in Cycles 7 and beyond (on Day 1).

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

Dosage and administration details:

Dexamethasone was given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle.

Number of subjects in period 1	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
Started	61
Response-evaluable Population	59
Completed	0
Not completed	61
Adverse event, serious fatal	22
Consent withdrawn by subject	8
Reason Not Specified	28
Lost to follow-up	2
Missing	1

Baseline characteristics

Reporting groups

Reporting group title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
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Reporting group description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

Reporting group values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg	Total	
Number of subjects	61	61	
Age Categorical Units: Subjects			

Age continuous			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: years			
arithmetic mean	67.8		
standard deviation	± 7.80	-	
Gender categorical			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: Subjects			
Male	32	32	
Female	29	29	
Race			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
White	53	53	
More than one race	0	0	
Not Reported	5	5	
Ethnicity			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	55	55	
Not Reported	5	5	
Unknown	0	0	

Weight			
Units: kilograms (kg)			
arithmetic mean	80.08		
standard deviation	± 17.625	-	
Height			
Number analyzed is the number of participants with data available for height at Baseline.			
Units: centimeters (cm)			
arithmetic mean			
standard deviation	±	-	

Subject analysis sets

Subject analysis set title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

Reporting group values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg		
Number of subjects	60		
Age Categorical			
Units: Subjects			

Age continuous			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: years			
arithmetic mean	0		
standard deviation	±		
Gender categorical			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: Subjects			
Male	0		
Female	0		
Race			
Safety population included participants who received at least 1 dose of any study treatment regimen.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	0		
Native Hawaiian or Other Pacific Islander	0		
White	0		
More than one race	0		
Not Reported	0		
Ethnicity			
Safety population included participants who received at least 1 dose of any study treatment regimen.			

Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Not Reported	0		
Unknown	0		
Weight			
Units: kilograms (kg)			
arithmetic mean			
standard deviation	±		
Height			
Number analyzed is the number of participants with data available for height at Baseline.			
Units: centimeters (cm)			
arithmetic mean	166.8		
standard deviation	± 8.71		

End points

End points reporting groups

Reporting group title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
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Reporting group description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

Subject analysis set title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

Primary: Percentage of Participants With Very Good Partial Response (VGPR) or Better (Complete Response + VGPR)

End point title	Percentage of Participants With Very Good Partial Response (VGPR) or Better (Complete Response + VGPR) ^[1]
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End point description:

Response was assessed using International Myeloma Working Group (IMWG) Criteria. VGPR is defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90 % or greater reduction in serum M-protein plus urine M-protein level <100 milligram (mg) per 24 hours. The percentage of participants were rounded off to the single decimal point. Response-evaluable population included participants who received at least 1 dose of ixazomib, had measurable disease during the screening period, and have at least 1 postbaseline disease assessment.

End point type	Primary
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End point timeframe:

Up to 5 years

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: percentage of participants				
number (confidence interval 95%)	32.2 (20.62 to 45.64)			

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Response (DOR)

End point title	Duration of Response (DOR) ^[2]
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End point description:

DOR is defined as the time from the date of first documentation of PR or better to the date of the first documented PD among participants who responded to the treatment. Response-evaluable population included participants who received at least 1 dose of ixazomib, had measurable disease during the screening period, and had at least 1 postbaseline disease assessment. The data is reported for responders.

End point type	Primary
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End point timeframe:

Up to 5 years

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: years				
median (confidence interval 95%)	24 (15.9 to 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
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End point description:

PFS is defined as time from date of first dose of drug to date of first documentation of progressive disease (PD) or death from any cause, whichever occurs first. Participant without documentation of PD or death were censored at the date of last response assessment that is SD or better. PD is defined as increase of 25% of lowest response value in one or more of following criteria: serum M-component (absolute increase ≥ 0.5 g/dl); or urine M-component (absolute increase ≥ 200 mg/24-hour); difference between involved and uninvolved FLC levels (absolute increase > 10 mg/dl); or bone marrow plasma cell percentage (absolute plasma cell percentage $\geq 10\%$); development of new/ increase in size of existing bone lesions or soft tissue plasmacytoma; or development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder. SD is defined as not meeting criteria for other responses. Safety population included participants who received at least 1 dose of any study treatment regimen.

End point type	Secondary
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End point timeframe:

Up to 5 years

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: months				
median (confidence interval 95%)	16.8 (10.1 to 23.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
ORR is defined as percentage of participants with complete response (CR), VGPR and partial response (PR). CR: Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; normal free light chain (FLC) ratio of 0.26-1.65; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein + urine M-protein level <100 mg/24 hours; and PR: ≥50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥90%/to <200 mg/24 hours; In addition, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas; no known evidence of progressive/new bone lesions. The percentage of participants were rounded off to the single decimal point. Response-evaluable population included participants who received at least 1 dose of ixazomib, had measurable disease during the screening period, and had at least 1 postbaseline disease assessment.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: percentage of participants				
number (not applicable)	66.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Response (TTR)

End point title	Time To Response (TTR)
End point description:	
TTR is defined as the time from first dose of any study drug treatment to the date of first documentation of PR or better. PR is defined as $\geq 50\%$ reduction of serum M protein and reduction in 24-hour urinary M protein by $\geq 90\%$ /to < 200 mg/24 hours; In addition, if present at baseline, $\geq 50\%$ reduction in size of soft tissue plasmacytomas; no known evidence of progressive/new bone lesions. Response-evaluable population included participants who received at least 1 dose of ixazomib, had measurable disease during the screening period, and had at least 1 postbaseline disease assessment.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: months				
median (confidence interval 95%)	2.7 (1.9 to 5.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	
TTP is defined as the time from the first dose of any study drug treatment to the date of the first documented PD. PD is defined as increase of 25% of lowest response value in one or more of following criteria: serum M-component (absolute increase ≥ 0.5 g/dl); or urine M-component (absolute increase ≥ 200 mg/24-hour); difference between involved and uninvolved FLC levels (absolute increase > 10 mg/dl); or bone marrow plasma cell percentage (absolute plasma cell percentage $\geq 10\%$); development of new/ increase in size of existing bone lesions or soft tissue plasmacytoma; or development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder. Safety population included participants who received at least 1 dose of any study treatment regimen.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethason e 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: months				
median (confidence interval 95%)	21.1 (10.2 to 27.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time from the date of first dose of any study drug treatment to the date of death. Participant without documentation of death at the time of analysis will be censored at the last visit at which s/he was known to be alive. Safety population included participants who received at least 1 dose of any study treatment regimen.	
End point type	Secondary
End point timeframe:	
Up to 5 years	

End point values	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethason e 20 mg			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: years				
median (confidence interval 95%)	-999999 (- 999999 to 999999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years

Adverse event reporting additional description:

Safety population included participants who received at least 1 dose of any study treatment regimen.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg
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Reporting group description:

Ixazomib, 4 mg, capsules, orally, on Days 1, 8 and 15 of each 28-day cycle along with daratumumab, 16 mg/kg, intravenously (IV), on Days 1, 8, 15 and 22 of Cycles 1 and 2, on Days 1 and 15 (every 2 weeks) for Cycles 3 to 6 and on Day 1 (every 4 weeks) for Cycle 7 and beyond along with dexamethasone, 20 mg, tablets, orally on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle until progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or up to 5 years.

Serious adverse events	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 61 (45.90%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events	5		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Influenza B virus test positive			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Monoclonal immunoglobulin present			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Parainfluenzae virus infection			

subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	2 / 61 (3.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
COVID-19 pneumonia				
subjects affected / exposed	3 / 61 (4.92%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Gastroenteritis				
subjects affected / exposed	2 / 61 (3.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal bacteraemia				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				
subjects affected / exposed	1 / 61 (1.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia herpes viral			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	58 / 61 (95.08%)		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 10		
Peripheral swelling subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 5		
Oedema peripheral subjects affected / exposed occurrences (all)	10 / 61 (16.39%) 15		
Fatigue subjects affected / exposed occurrences (all)	15 / 61 (24.59%) 25		
Pyrexia subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 9		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4		
Productive cough subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 8		
Dyspnoea subjects affected / exposed occurrences (all)	10 / 61 (16.39%) 14		
Cough			

subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 12		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 11		
Investigations White blood cell count decreased subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 7		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Infusion related reaction subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 22 4 / 61 (6.56%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4 4 / 61 (6.56%) 4 4 / 61 (6.56%) 4 6 / 61 (9.84%) 9 6 / 61 (9.84%) 9 4 / 61 (6.56%) 4		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 61 (27.87%)		
occurrences (all)	33		
Thrombocytopenia			
subjects affected / exposed	16 / 61 (26.23%)		
occurrences (all)	35		
Neutropenia			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	6		
Leukopenia			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	8		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Eye disorders			
Cataract			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 61 (21.31%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	26 / 61 (42.62%)		
occurrences (all)	43		
Constipation			
subjects affected / exposed	10 / 61 (16.39%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		

Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 11		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5 4 / 61 (6.56%) 5 14 / 61 (22.95%) 20 14 / 61 (22.95%) 23 4 / 61 (6.56%) 5		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 14 6 / 61 (9.84%) 13 4 / 61 (6.56%) 4 5 / 61 (8.20%) 5 5 / 61 (8.20%) 5		

Bronchitis subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 10		
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 7		
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 5		
Hyperglycaemia subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2019	The following changes were implemented with Amendment 2: 1. Added a hepatitis B virus (HBV) testing requirement for all potential and enrolled participants. 2. Added reactivation of HBV, a potential risk newly associated with daratumumab use, as a reason for daratumumab discontinuation. 3. Noted that clinically indicated therapy for HBV reactivation was permitted in affected participants. 4. Added reactivation of HBV, a potential risk newly associated with daratumumab use, as a clinical event that may need to be managed. 5. Specified that participants undergoing monitoring for HBV reactivation must come to the clinic for their overall survival follow-up visits. 6. Removed mention of next-generation flow cytometry (NGF) methodology, which was no longer planned to be used in this study to assess minimal residual disease (MRD).
28 September 2020	The following changes were implemented with Amendment 4: 1. Simplified the schedule of events to reflect the fact that all study participants were in Cycle 13 of treatment (or later, at the time of this amendment), as well as to reflect other changes noted. 2. Updated language about management of clinical events in participants receiving ixazomib. 3. Removed mention of "breakthrough therapy" designation for relapsed or refractory amyloid light chain (AL) amyloidosis in the United States (US).
30 March 2022	The following changes were implemented with Amendment 7: 1. Added a new schedule of events for future use, after the final analysis has been conducted. 2. Added language on local clinical laboratory evaluations for efficacy and safety after implementation of Amendment 7. 3. Updated the Management of Clinical Events section for ixazomib to reflect evolving data, including the addition that ixazomib should be discontinued if Stevens-Johnson syndrome (SJS) occurs. 4. Updated the terms of the Posttrial Access program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported