



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 |
|-----------------------|--------|

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 |
|-----------|--|

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 |
|-----------------------|--|

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 |
|-----------------------|--|

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 |
|----------------------------|--|

| | |
|---------------------------|-----------------|
| 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.

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] |
|-----------------|---|

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 |
|----------------|---------|

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] |
|-----------------|---|

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 |
|----------------|---------|

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) |
|-----------------|---------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Ixazomib 4 mg + Daratumumab 16 mg/kg + Dexamethasone 20 mg |
|-----------------------|--|

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 | | |

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

| | | | |
|--|---|--|--|
| 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