



Clinical trial results:

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant Summary

| | |
|--------------------------|---|
| EudraCT number | 2013-002076-41 |
| Trial protocol | BE CZ SE DK IT PT ES AT HU DE NL GR PL NO |
| Global end of trial date | 08 September 2023 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 22 September 2024 |
| First version publication date | 22 September 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | C16019 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02181413 |
| WHO universal trial number (UTN) | U1111-1155-8695 |
| Other trial identifiers | Israel MOH: C16019CTIL, CCMO: NL.47795.029.14, HC-CTD: 173116, TCTIN: 1036024001, SNCTP: SNCTP000001745 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Takeda |
| Sponsor organisation address | 95 Hayden Avenue, Lexington, United States, MA 02421 |
| Public contact | Study Director, Takeda, N/A N/A, TrialDisclosures@takeda.com |
| Scientific contact | Study Director, Takeda, N/A N/A, 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 | 08 September 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 September 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in participants with newly diagnosed multiple myeloma (NDMM) who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT).

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|------------------|
| Actual start date of recruitment | 16 July 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 83 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 28 |
| Country: Number of subjects enrolled | Japan: 22 |
| Country: Number of subjects enrolled | Korea, Republic of: 40 |
| Country: Number of subjects enrolled | Singapore: 12 |
| Country: Number of subjects enrolled | Taiwan: 13 |
| Country: Number of subjects enrolled | Thailand: 6 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Czechia: 42 |
| Country: Number of subjects enrolled | Denmark: 31 |
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Germany: 76 |
| Country: Number of subjects enrolled | Greece: 60 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | Israel: 22 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Italy: 50 |
| Country: Number of subjects enrolled | Netherlands: 19 |
| Country: Number of subjects enrolled | Norway: 19 |
| Country: Number of subjects enrolled | Poland: 15 |
| Country: Number of subjects enrolled | Portugal: 10 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Spain: 38 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | Türkiye: 20 |
| Country: Number of subjects enrolled | Ukraine: 3 |
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Brazil: 8 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 656 |
| EEA total number of subjects | 428 |

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) | 525 |
| From 65 to 84 years | 131 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants enrolled at 167 sites globally to take part in this study from 16 July 2014 to 8 September 2023.

Pre-assignment

Screening details:

Participants with newly diagnosed multiple myeloma (NDMM) who underwent induction therapy according to regional standard of care (SoC), followed by high-dose melphalan (200 milligrams per meter square [mg/m²]) and Autologous Stem Cell Transplant (ASCT) were enrolled in a 3:2 ratio to receive ixazomib citrate or placebo.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until progressive disease (PD), unacceptable toxicity, or discontinuation for alternate reasons.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

On Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons.

| | |
|------------------|------------------|
| Arm title | Ixazomib Citrate |
|------------------|------------------|

Arm description:

Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to adverse events (AEs) were not dose escalated.

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

Dosage and administration details:

Ixazomib citrate 3 mg, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons

| Number of subjects in period 1 | Placebo | Ixazomib Citrate |
|---------------------------------------|---------|------------------|
| Started | 261 | 395 |
| Intent-to-Treat (ITT) Population | 261 | 395 |
| Safety Population | 259 | 394 |
| Per Protocol (PP) Population | 256 | 387 |
| Completed | 206 | 322 |
| Not completed | 55 | 73 |
| Consent withdrawn by subject | 45 | 61 |
| Reason Not Specified | 2 | 5 |
| Lost to follow-up | 8 | 7 |

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Placebo |
| Reporting group description: Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until progressive disease (PD), unacceptable toxicity, or discontinuation for alternate reasons. | |
| Reporting group title | Ixazomib Citrate |
| Reporting group description: Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to adverse events (AEs) were not dose escalated. | |

| Reporting group values | Placebo | Ixazomib Citrate | Total |
|------------------------------------|---------|------------------|-------|
| Number of subjects | 261 | 395 | 656 |
| Age Categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 58.2 ± 7.92 | 56.8 ± 8.17 | - |
| Gender categorical Units: Subjects | | | |
| Male | 162 | 252 | 414 |
| Female | 99 | 143 | 242 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 11 | 14 | 25 |
| Not Hispanic or Latino | 240 | 362 | 602 |
| Unknown or Not Reported | 10 | 19 | 29 |
| Race/Ethnicity Units: Subjects | | | |
| White | 213 | 315 | 528 |
| Black or African American | 3 | 7 | 10 |
| Asian | 36 | 59 | 95 |
| Other | 1 | 2 | 3 |
| Not Reported | 8 | 12 | 20 |
| Region of Enrollment Units: Subjects | | | |
| Australia | 11 | 17 | 28 |
| Japan | 9 | 13 | 22 |
| Korea, Republic of | 17 | 23 | 40 |
| Singapore | 4 | 8 | 12 |
| Taiwan | 3 | 10 | 13 |
| Thailand | 1 | 5 | 6 |
| Austria | 2 | 2 | 4 |
| Belgium | 5 | 5 | 10 |

| | | | |
|---|----------|----------|----|
| Czech Republic | 12 | 30 | 42 |
| Denmark | 11 | 20 | 31 |
| France | 7 | 11 | 18 |
| Germany | 26 | 50 | 76 |
| Greece | 22 | 38 | 60 |
| Hungary | 9 | 16 | 25 |
| Israel | 12 | 10 | 22 |
| Italy | 26 | 24 | 50 |
| Netherlands | 11 | 8 | 19 |
| Norway | 6 | 13 | 19 |
| Poland | 5 | 10 | 15 |
| Portugal | 2 | 8 | 10 |
| South Africa | 4 | 3 | 7 |
| Spain | 19 | 19 | 38 |
| Sweden | 4 | 7 | 11 |
| Switzerland | 3 | 0 | 3 |
| Turkey | 10 | 10 | 20 |
| Ukraine | 2 | 1 | 3 |
| United Kingdom | 14 | 21 | 35 |
| Argentina | 0 | 3 | 3 |
| Brazil | 3 | 5 | 8 |
| United States | 1 | 5 | 6 |
| Height | | | |
| Number analysed is the number of participants with available height data. | | | |
| Units: centimeter (cm) | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | - |
| Body Surface Area (BSA) | | | |
| Number analysed is the number of participants with available BSA data. | | | |
| Units: meter per square (m ²) | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | - |
| Weight | | | |
| Number analysed is the number of participants with available weight data. | | | |
| Units: kilogram (kg) | | | |
| arithmetic mean | 75.18 | 75.93 | |
| standard deviation | ± 14.648 | ± 15.989 | - |

Subject analysis sets

| | |
|----------------------------|---------------|
| Subject analysis set title | Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until progressive disease (PD), unacceptable toxicity, or discontinuation for alternate reasons.

| | |
|----------------------------|------------------|
| Subject analysis set title | Ixazomib citrate |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to adverse events (AEs) were not dose escalated.

| Reporting group values | Placebo | Ixazomib citrate | |
|------------------------|---------|------------------|--|
| Number of subjects | 256 | 388 | |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------------|---|---|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Male | 0 | 0 | |
| Female | 0 | 0 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | |
| Not Hispanic or Latino | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |
| Race/Ethnicity | | | |
| Units: Subjects | | | |
| White | 0 | 0 | |
| Black or African American | 0 | 0 | |
| Asian | 0 | 0 | |
| Other | 0 | 0 | |
| Not Reported | 0 | 0 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Australia | 0 | 0 | |
| Japan | 0 | 0 | |
| Korea, Republic of | 0 | 0 | |
| Singapore | 0 | 0 | |
| Taiwan | 0 | 0 | |
| Thailand | 0 | 0 | |
| Austria | 0 | 0 | |
| Belgium | 0 | 0 | |
| Czech Republic | 0 | 0 | |
| Denmark | 0 | 0 | |
| France | 0 | 0 | |
| Germany | 0 | 0 | |
| Greece | 0 | 0 | |
| Hungary | 0 | 0 | |
| Israel | 0 | 0 | |
| Italy | 0 | 0 | |
| Netherlands | 0 | 0 | |
| Norway | 0 | 0 | |
| Poland | 0 | 0 | |
| Portugal | 0 | 0 | |
| South Africa | 0 | 0 | |
| Spain | 0 | 0 | |
| Sweden | 0 | 0 | |

| | | | |
|---|----------|----------|--|
| Switzerland | 0 | 0 | |
| Turkey | 0 | 0 | |
| Ukraine | 0 | 0 | |
| United Kingdom | 0 | 0 | |
| Argentina | 0 | 0 | |
| Brazil | 0 | 0 | |
| United States | 0 | 0 | |
| Height | | | |
| Number analysed is the number of participants with available height data. | | | |
| Units: centimeter (cm) | | | |
| arithmetic mean | 168.73 | 169.71 | |
| standard deviation | ± 10.347 | ± 10.004 | |
| Body Surface Area (BSA) | | | |
| Number analysed is the number of participants with available BSA data. | | | |
| Units: meter per square (m^2) | | | |
| arithmetic mean | 1.87 | 1.88 | |
| standard deviation | ± 0.221 | ± 0.235 | |
| Weight | | | |
| Number analysed is the number of participants with available weight data. | | | |
| Units: kilogram (kg) | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |

End points

End points reporting groups

| | |
|---|------------------|
| Reporting group title | Placebo |
| Reporting group description: Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until progressive disease (PD), unacceptable toxicity, or discontinuation for alternate reasons. | |
| Reporting group title | Ixazomib Citrate |
| Reporting group description: Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to adverse events (AEs) were not dose escalated. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until progressive disease (PD), unacceptable toxicity, or discontinuation for alternate reasons. | |
| Subject analysis set title | Ixazomib citrate |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to adverse events (AEs) were not dose escalated. | |

Primary: Progression Free Survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression Free Survival (PFS) |
| End point description: PFS was defined as the time from the date of randomisation to the date of first documentation of PD, as evaluated by an independent review committee (IRC) according to International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurred first. PD was defined as $\geq 25\%$ increase from lowest value in: serum/urine M component; participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain (FLC) levels must be >10 milligrams per deciliter (mg/dL); participants without measurable serum, urine M-protein levels and FLC levels, bone marrow plasma cell percent must have been $\geq 10\%$; new bone lesions/soft tissue plasmacytomas development/existing bone lesions/soft tissue plasmacytomas size increase; hypercalcemia development. Intent-to-Treat (ITT) Population was defined as all participants who were randomised and had post randomisation data. | |
| End point type | Primary |
| End point timeframe: Randomisation up to End of treatment (EOT) (24 months); thereafter followed up every 4 weeks until progression of disease or death (up to 4 years) | |

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 21.3 (17.97 to 24.67) | 26.5 (23.69 to 33.81) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Progression Free Survival (PFS) |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.582 |
| upper limit | 0.89 |

Notes:

[1] - P-value was based on log-rank test stratified by pre-induction regimen, International Staging System (ISS) stage and response after transplantation.

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was measured as the time from the date of randomisation to the date of death. '99999' indicates median and upper limit of 95% confidence interval (CI) were not estimable due to low number of participants with events. ITT Population was defined as all participants who were randomised and had post randomisation data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to end of follow up period (up to 107 months)

| | | | | |
|----------------------------------|------------------------|-------------------------|--|--|
| End point values | Placebo | Ixazomib Citrate | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (96.95 to 99999) | 99999 (104.97 to 99999) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Overall Survival (OS) |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.025 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.789 |
| upper limit | 1.332 |

Notes:

[2] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Percentage of Participants With Any Best Response Category Before PD or Subsequent Therapy

| | |
|-----------------|--|
| End point title | Percentage of Participants With Any Best Response Category Before PD or Subsequent Therapy |
|-----------------|--|

End point description:

Response was assessed according to IMWG criteria. Best response includes partial response (PR), very good partial response (VGPR) and complete response (CR). PR as per IMWG criteria is 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to less than ($<$)200 milligrams (mg) per 24 hours. VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours. CR is negative immunofixation of serum and urine and disappearance of soft tissue plasmacytomas and $< 5\%$ plasma cells in bone marrow. Stringent CR (sCR) is CR and normal FLC ratio and absence of clonal plasma cells (PCs) by immunohistochemistry or 2 to 4-color flow cytometry. ITT Population was defined as all participants who were randomised and had post randomisation data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to EOT (up to 24 months) and thereafter every 4 weeks until initiation of the next line of therapy (up to 107 months)

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| PR | 14 | 11 | | |
| VGPR | 11 | 11 | | |
| CR | 6 | 5 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | CR |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.37 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.732 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.365 |
| upper limit | 1.466 |

Notes:

[3] - P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by pre-induction regimen, pre-induction international staging system (ISS), and response after transplantation at screening

Secondary: Second Progression Free Survival (PFS2)

| | |
|-----------------|---|
| End point title | Second Progression Free Survival (PFS2) |
|-----------------|---|

End point description:

PFS2 is defined as the time from the date of randomisation to the date of objective disease progression on next line treatment or death from any cause (whichever occurs first). PD is defined as ≥25% increase from lowest value in: serum/urine M-component; participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels must be >10 mg/dL; participants without measurable serum, urine M-protein levels and FLC levels, bone marrow plasma cell percent must be ≥10%; new bone lesions/soft tissue plasmacytomas development/existing bone lesions/soft tissue plasmacytomas size rise; hypercalcaemia development. '99999' indicates upper limit of 95% CI was not estimable due to low number of participants with events. ITT Population was defined as all participants who were randomised and had post randomisation data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to EOT (up to 24 months); thereafter followed up every 4 weeks until initiation of next-line therapy and then every 12 weeks until second progressive disease (PD2) or death (up to 107 months)

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 80.4 (68.7 to 99999) | 84.0 (67.22 to 99999) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Second Progression Free Survival (PFS2) |
| Comparison groups | Placebo v Ixazomib Citrate |

| | |
|---|------------------------|
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.902 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.015 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.795 |
| upper limit | 1.298 |

Notes:

[4] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Time to Progression (TTP)

| | |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

TTP is defined as the time from the date of randomisation to the date of first documentation of PD, using IMWG criteria. PD is defined as ≥25% increase from lowest value in: serum/urine M-component; participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels must be >10 mg/dL; participants without measurable serum, urine M-protein levels and FLC levels, bone marrow plasma cell percent must be ≥10%; new bone lesions/soft tissue plasmacytomas development/existing bone lesions/soft tissue plasmacytomas size rise; hypercalcaemia development. Participants without documentation of PD at the time of analysis were censored at the date of last response assessment that is stable disease or better. ITT Population was defined as all participants who were randomised and had post randomisation data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to PD (up to 107 months)

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 21.4 (18.10 to 24.67) | 26.6 (23.69 to 33.81) | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Time to Progression (TTP) |
| Comparison groups | Placebo v Ixazomib Citrate |

| | |
|---|------------------------|
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.716 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.579 |
| upper limit | 0.886 |

Notes:

[5] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Time to End of the Next Line of Therapy

| | |
|--|---|
| End point title | Time to End of the Next Line of Therapy |
| End point description: | |
| Time to end of the next line of therapy was defined as the time from the date of randomisation to the date of last dose of the next line of antineoplastic therapy following study treatment or death due to any cause, whichever occurred first or date of last contact for participants who never took antineoplastic therapy. ITT Population was defined as all participants who were randomised and had post randomisation data. | |
| End point type | Secondary |
| End point timeframe: | |
| Randomisation up to 107 months | |

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 50.4 (42.84 to 61.01) | 55.9 (49.61 to 61.86) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to End of the Next Line of Therapy |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.431 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.922 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.753 |
| upper limit | 1.129 |

Notes:

[6] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Time to Start of the Next Line of Therapy

| | |
|-----------------|---|
| End point title | Time to Start of the Next Line of Therapy |
|-----------------|---|

End point description:

Time to start of the next line of therapy was defined as the time from the date of randomisation to the date of initiation dose of the next line of antineoplastic therapy following study treatment or death due to any cause, whichever occurs first. Participants who never took antineoplastic therapy were censored at the date of last contact or death. ITT Population was defined as all participants who were randomised and had post randomisation data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 261 | 395 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 27.6 (24.48 to 31.61) | 33.1 (29.14 to 36.34) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to Start of the Next Line of Therapy |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 ^[7] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.833 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.005 |

Notes:

[7] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Percentage of Participants Who Develop A New Primary Malignancy

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Develop A New Primary Malignancy |
|-----------------|---|

End point description:

The decimal values of percentages were subjected to rounding off. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 394 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 8 | 7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of the Next Line of Therapy

| | |
|-----------------|--------------------------------------|
| End point title | Duration of the Next Line of Therapy |
|-----------------|--------------------------------------|

End point description:

Duration of the next line of therapy is defined as the time from the date of the first dose of the next line of therapy to the date of the last dose of the next antineoplastic therapy following study treatment or death due to any cause, whichever occurred first. Duration of the next line of therapy was analysed on those participants who actually received and completed the next line of therapy following the study treatment and duration would be summarized using Kaplan-Meier method. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed indicates the number of participants who started next line of therapy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 187 | 278 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.3 (9.82 to 16.53) | 9.6 (7.49 to 12.06) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Duration of the Next Line of Therapy |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.179 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.959 |
| upper limit | 1.45 |

Secondary: Number of Participants With Maintenance of MRD Negativity

| | |
|--|---|
| End point title | Number of Participants With Maintenance of MRD Negativity |
| End point description: MRD negativity is defined as absence of MRD and MRD positivity is defined as presence of MRD. The maintenance of MRD negativity up to the end of treatment was assessed and reported in participants converting from MRD+ at Baseline to MRD negative. Bone marrow aspirates and blood samples were sent to a central laboratory and were assessed for MRD using flow cytometry and a sequencing methodology. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed is the number of participants who converted from MRD+ at Baseline to MRD negative. | |
| End point type | Secondary |
| End point timeframe: Up to EOT (up to 24 months) | |

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 39 | | |
| Units: participants | 25 | 37 | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Maintenance of MRD Negativity |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.805 [8] |
| Method | Fisher exact |

Notes:

[8] - P-value was based on Fisher's exact test comparing conversion to MRD- at any time post study entry between treatment groups.

Secondary: Number of Participants With Conversion to Minimal Residual Disease (MRD) Negative

| | |
|---|---|
| End point title | Number of Participants With Conversion to Minimal Residual Disease (MRD) Negative |
| End point description: MRD negativity (MRD-) is defined as absence of MRD and MRD positivity (MRD+) is defined as presence of MRD. The conversion rate from MRD positive to MRD negative was assessed and reported. Bone marrow aspirates and blood samples were sent to a central laboratory and were assessed for MRD using flow cytometry and a sequencing methodology. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed indicates the number of participants with MRD+ at Baseline. | |
| End point type | Secondary |
| End point timeframe: Baseline up to EOT (up to 24 months) | |

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 139 | 225 | | |
| Units: participants | 27 | 39 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Conversion to MRD- |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 364 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.814 [9] |
| Method | Fisher exact |

Notes:

[9] - P-value was based on Fisher's exact test comparing conversion to MRD- at any time post study entry between treatment groups.

Secondary: Correlation Between MRD Status and Progression Free Survival (PFS)

| | |
|--|--|
| End point title | Correlation Between MRD Status and Progression Free Survival (PFS) |
| End point description: PFS is defined as the time from the date of randomisation to the date of first documentation of PD as evaluated by an IRC according to IMWG criteria, or death due to any cause, whichever occurred first, assessed for up to 107 months in this outcome measure. '99999' indicates upper limit of 95% CI was not estimable due to censoring. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed is the number of participants with data available for analyses. 'n' indicates the number of participants available for analysis in the specified category. | |

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomisation up to 107 months | |

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 214 | 342 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| MRD- at Study Entry (n=75,117) | 32.5 (19.32 to 99999) | 38.6 (33.81 to 99999) | | |
| MRD+ at Study Entry (n=139,225) | 18.5 (15.70 to 21.91) | 23.1 (20.24 to 25.69) | | |

Statistical analyses

| Statistical analysis title | MRD- at Study Entry |
|---|----------------------------|
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 556 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.034 ^[10] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.612 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.386 |
| upper limit | 0.969 |

Notes:

[10] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

| Statistical analysis title | MRD+ at Study Entry |
|---|----------------------------|
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 556 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 ^[11] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.704 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.539 |
| upper limit | 0.92 |

Notes:

[11] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: Correlation Between MRD Status and Overall Survival (OS)

| | |
|-----------------|--|
| End point title | Correlation Between MRD Status and Overall Survival (OS) |
|-----------------|--|

End point description:

OS was measured as the time from the date of randomisation to the date of death, assessed for up to 107 months in this outcome measure.

'99999' indicates median, lower limit, and upper limit of 95% CI were not estimable due to censoring.

ITT Population was defined as all participants who were randomised and had post randomisation data.

Subjects analysed is the number of participants with data available for analyses. 'n' indicates the number of participants available for analysis in the specified category.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 214 | 342 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| MRD- at Study Entry (n=75,117) | 99999 (84.90 to 99999) | 99999 (99999 to 99999) | | |
| MRD+ at Study Entry (n=139,225) | 99999 (90.74 to 99999) | 105.0 (91.47 to 99999) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | MRD- at Study Entry |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 556 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.182 ^[12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.414 |
| upper limit | 1.184 |

Notes:

[12] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

| | |
|---|----------------------------|
| Statistical analysis title | MRD+ at Study Entry |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 556 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.847 ^[13] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.966 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.682 |
| upper limit | 1.368 |

Notes:

[13] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: OS Benefits in a High-Risk Population

| | |
|-----------------|---------------------------------------|
| End point title | OS Benefits in a High-Risk Population |
|-----------------|---------------------------------------|

End point description:

High-risk population included but was not limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. OS was measured as the time from the date of randomisation to the date of death. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed is the number of participants present in the high-risk group. '99999' indicates that upper limit of 95% CI was not estimable due to low number of participants with events.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomisation up to 107 months

| | | | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| End point values | Placebo | Ixazomib Citrate | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 61 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 69.0 (33.25 to 92.98) | 64.2 (40.97 to 99999) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | OS Benefits in a HIgh-Risk Population |
| Comparison groups | Placebo v Ixazomib Citrate |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.905 ^[14] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.583 |
| upper limit | 1.613 |

Notes:

[14] - P-value was based on log-rank test stratified by pre-induction regimen, ISS stage and response after transplantation.

Secondary: PFS Benefits in a High-Risk Population

| | |
|--|--|
| End point title | PFS Benefits in a High-Risk Population |
| End point description: | |
| High-risk population included but not be limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. PFS= time from date of randomisation to the date of first documentation of PD, as evaluated by an IRC according to IMWG criteria, or death due to any cause (whichever occurs first). PD= ≥25% increase from lowest value in: serum/urine M-component; participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels must be >10 mg/dL; participants without measurable serum, urine M-protein levels and FLC levels, bone marrow plasma cell percent must be ≥10%; new bone lesions/soft tissue plasmacytomas development/existing bone lesions/soft tissue plasmacytomas size rise; hypercalcaemia development. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed is the number of participants present in the high-risk group. | |
| End point type | Secondary |
| End point timeframe: | |
| Randomisation up to 107 months | |

| | | | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| End point values | Placebo | Ixazomib Citrate | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 61 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 16.8 (12.81 to 18.50) | 18.5 (12.06 to 31.15) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience at Least One Treatment

Emergent Adverse Event (TEAE) or Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Participants Who Experience at Least One Treatment Emergent Adverse Event (TEAE) or Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject administered a drug. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. A TEAE was defined as an AE that started or worsened after first study drug administration and within 30 days of last dose of study drug. An SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital abnormality or birth defect, an important medical event. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 394 | | |
| Units: participants | | | | |
| TEAEs | 241 | 382 | | |
| SAEs | 51 | 108 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Score

| | |
|-----------------|---|
| End point title | Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Score |
|-----------------|---|

End point description:

ECOG performance status assesses a participant's performance status on a 6-point scale ranging from 0=fully active/able to carry on all pre-disease activities without restriction; 1=restricted in physically strenuous activity, ambulatory/able to carry out light or sedentary work; 2=ambulatory (>50% of waking hours), capable of all self-care, unable to carry out any work activities; 3=capable of only limited self-care, confined to bed/chair >50% of waking hours; 4=completely disabled, cannot carry on any self-care, totally confined to bed/chair; 5=dead. Lower scores indicate improvement. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo. Subjects analysed indicates the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to EOT (up to Month 24)

| End point values | Placebo | Ixazomib Citrate | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 371 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 0.63) | 0.0 (± 0.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Ixazomib

| | |
|-----------------|--|
| End point title | Plasma Concentration of Ixazomib ^[15] |
|-----------------|--|

End point description:

Plasma concentrations of the complete hydrolysis product of ixazomib citrate (ixazomib) were measured using a validated Liquid Chromatography-tandem Mass Spectrometry (LC/MS/MS) assay. The Pharmacokinetic (PK) Analysis Population was defined as participants with at least one PK sample that was collected and analysed. 'n' indicates the number of participants with data available for analysis at the specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 of Cycle 1: 1 hour and 4 hour post-dose; Predose on Days 8 and 15 of Cycle 1, Days 1 and 8 of Cycle 2, Day 1 of Cycles 3 through 10 (each cycle length= 28 days)

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: Only the drug-treated Ixazomib Citrate arm was to be analysed for this endpoint.

| End point values | Ixazomib Citrate | | | |
|--|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 393 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1: 1 Hour Post-dose (n=381) | 27.919 (± 24.7787) | | | |
| Cycle 1 Day 1: 4 Hours Post-dose (n=383) | 10.352 (± 9.8078) | | | |
| Cycle 1 Day 8 (n=387) | 1.584 (± 1.6707) | | | |
| Cycle 1 Day 15 (n=382) | 2.611 (± 1.4305) | | | |
| Cycle 2 Day 1 (n=384) | 1.946 (± 1.0984) | | | |
| Cycle 2 Day 8 (n=374) | 3.232 (± 2.0069) | | | |
| Cycle 3 Day 1 (n=367) | 2.258 (± 1.1508) | | | |
| Cycle 4 Day 1 (n=367) | 2.396 (± 1.7822) | | | |
| Cycle 5 Day 1 (n=360) | 2.400 (± 1.4921) | | | |
| Cycle 6 Day 1 (n=350) | 2.623 (± 1.6994) | | | |

| | | | | |
|------------------------|-----------------------|--|--|--|
| Cycle 7 Day 1 (n=349) | 2.691 (\pm 1.9842) | | | |
| Cycle 8 Day 1 (n=338) | 2.637 (\pm 1.7074) | | | |
| Cycle 9 Day 1 (n=327) | 2.610 (\pm 1.9380) | | | |
| Cycle 10 Day 1 (n=321) | 2.594 (\pm 1.9509) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-related Quality of Life (HRQL) Score Based on The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Quality of Life Domain

| | |
|-----------------|---|
| End point title | Change From Baseline in Health-related Quality of Life (HRQL) Score Based on The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Quality of Life Domain |
|-----------------|---|

End point description:

EORTC QLQ-C30 is cancer-specific instrument that contains 30 items & provides multidimensional assessment of HRQL. EORTC QLQ-C30 includes global health status/quality of life (GHS/QOL), functional scales (physical, role, cognitive, emotional, social), symptom scales (fatigue, pain, nausea/vomiting), & 6 single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Most questions from QLQ-C30 are 4-point scale (1/Not at All to 4/Very Much), except Items 29-30, which comprise GHS scale & are 7-point scale (1/Very Poor to 7/Excellent). GHS total score= $([\{Q29+Q30\}/2]-1)/6*100$. Answers are converted into grading scale, with values between 0 (worse outcome) to 100 (best outcome). High score represents a favorable outcome with best quality of life for participant. ITT Population was defined as all participants who were randomised and had post randomisation data. Subjects analysed indicates the number of participants with data available for analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to EOT (up to Month 24)

| End point values | Placebo | Ixazomib Citrate | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 237 | 349 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.7 (\pm 1.57) | -4.1 (\pm 1.43) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Change From Baseline in HRQL Score |
| Comparison groups | Placebo v Ixazomib Citrate |

| | |
|---|------------------------------------|
| Number of subjects included in analysis | 586 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.074 ^[16] |
| Method | Logrank |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.9 |
| upper limit | 0.2 |

Notes:

[16] - P-value was from the significance test for the coefficient of the interaction between treatment and visit.

Secondary: Number of Participants With Markedly Abnormal Clinical Laboratory Values Reported as TEAEs

| | |
|-----------------|--|
| End point title | Number of Participants With Markedly Abnormal Clinical Laboratory Values Reported as TEAEs |
|-----------------|--|

End point description:

Laboratory tests included chemistry, hematology and urinalysis. Abnormal laboratory value was assessed as an AE if the value led to discontinuation or delay in treatment, dose modification, therapeutic intervention, or was considered by the investigator to be a clinically significant change from baseline. A TEAE was defined as an AE that started or worsened after first study drug administration and within 30 days of last dose of study drug. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 107 months

| End point values | Placebo | Ixazomib Citrate | | |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 259 | 394 | | |
| Units: subjects | 36 | 81 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Peripheral Neuropathy (PN) Events

| | |
|-----------------|---|
| End point title | Time to Resolution of Peripheral Neuropathy (PN) Events |
|-----------------|---|

End point description:

Peripheral neuropathy is defined as the TEAE in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is less than the maximum grade. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date,

whichever occurs first. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo. Subjects analysed indicates the number of participants with peripheral neuropathy events.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 107 months | |

| End point values | Placebo | Ixazomib Citrate | | |
|----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 73 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 159.0 (45.0 to 736.0) | 225.0 (117.0 to 421.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of PN Events

| | |
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| End point title | Time to Improvement of PN Events |
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End point description:

PN is defined as the TEAE in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to the Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is less than the maximum grade. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first. Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo. Subjects analysed indicates number of participants with peripheral neuropathy events.

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| End point type | Secondary |
| End point timeframe: | |
| Up to 107 months | |

| End point values | Placebo | Ixazomib Citrate | | |
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| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 | 73 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 130.0 (36.0 to 520.0) | 134.0 (70.0 to 252.0) | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization up to end of follow up period (107 months)

Adverse event reporting additional description:

All cause-mortality: ITT Population was defined as all participants who were randomized and had post randomization data. Serious and Other Adverse Events: Safety Population was defined as participants who received at least 1 dose of ixazomib citrate or placebo.

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| Assessment type | Systematic |
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Dictionary used

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| Dictionary name | MedDRA |
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| Dictionary version | 26.0 |
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Reporting groups

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| Reporting group title | Ixazomib Citrate |
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Reporting group description:

Ixazomib citrate 3 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons. Participants who had any dose reductions due to AEs were not dose escalated.

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| Reporting group title | Placebo |
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Reporting group description:

Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 26 until PD, unacceptable toxicity, or discontinuation for alternate reasons.

| Serious adverse events | Ixazomib Citrate | Placebo | |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 108 / 394 (27.41%) | 51 / 259 (19.69%) | |
| number of deaths (all causes) | 144 | 93 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasma cell leukaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leiomyoma | | | |

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| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cancer | | | |

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| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 394 (1.27%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Light chain analysis increased | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza B virus test positive | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone contusion | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Ligament sprain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulnar nerve injury | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

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| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radicular pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

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| Anaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Enteritis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontal disease | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema nodosum | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kyphosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 4 / 394 (1.02%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 394 (1.02%) | 2 / 259 (0.77%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Picornavirus infection | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 394 (0.76%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 394 (0.51%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia parainfluenzae viral | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 25 / 394 (6.35%) | 10 / 259 (3.86%) | |
| occurrences causally related to treatment / all | 7 / 30 | 2 / 16 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pneumococcal sepsis | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 394 (0.00%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 0 / 259 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 394 (0.25%) | 1 / 259 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Ixazomib Citrate | Placebo | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 371 / 394 (94.16%) | 229 / 259 (88.42%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 19 / 259 (7.34%) | |
| occurrences (all) | 23 | 22 | |
| Nervous system disorders | | | |

| | | | |
|---|--------------------------|-------------------------|--|
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 41 / 394 (10.41%) 57 | 23 / 259 (8.88%) 26 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 27 / 394 (6.85%) 31 | 8 / 259 (3.09%) 8 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 40 / 394 (10.15%) 49 | 19 / 259 (7.34%) 23 | |
| Headache subjects affected / exposed occurrences (all) | 43 / 394 (10.91%) 86 | 23 / 259 (8.88%) 38 | |
| Dizziness subjects affected / exposed occurrences (all) | 33 / 394 (8.38%) 49 | 18 / 259 (6.95%) 20 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 28 / 394 (7.11%) 35 | 8 / 259 (3.09%) 11 | |
| Neutropenia subjects affected / exposed occurrences (all) | 24 / 394 (6.09%) 33 | 15 / 259 (5.79%) 16 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 40 / 394 (10.15%) 68 | 6 / 259 (2.32%) 6 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 79 / 394 (20.05%) 108 | 43 / 259 (16.60%) 52 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 37 / 394 (9.39%) 57 | 18 / 259 (6.95%) 30 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 34 / 394 (8.63%) 44 | 11 / 259 (4.25%) 13 | |
| Pyrexia | | | |

| | | | |
|--|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 78 / 394 (19.80%) 190 | 37 / 259 (14.29%) 56 | |
| Asthenia subjects affected / exposed occurrences (all) | 30 / 394 (7.61%) 43 | 17 / 259 (6.56%) 21 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 135 / 394 (34.26%) 265 | 61 / 259 (23.55%) 160 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 13 / 394 (3.30%) 17 | 15 / 259 (5.79%) 15 | |
| Nausea subjects affected / exposed occurrences (all) | 154 / 394 (39.09%) 292 | 40 / 259 (15.44%) 111 | |
| Vomiting subjects affected / exposed occurrences (all) | 105 / 394 (26.65%) 219 | 28 / 259 (10.81%) 44 | |
| Constipation subjects affected / exposed occurrences (all) | 41 / 394 (10.41%) 47 | 21 / 259 (8.11%) 29 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough subjects affected / exposed occurrences (all) | 26 / 394 (6.60%) 34 | 9 / 259 (3.47%) 16 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 29 / 394 (7.36%) 35 | 18 / 259 (6.95%) 26 | |
| Cough subjects affected / exposed occurrences (all) | 87 / 394 (22.08%) 123 | 55 / 259 (21.24%) 87 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 35 / 394 (8.88%) 39 | 19 / 259 (7.34%) 26 | |
| Rash maculo-papular | | | |

| | | | |
|---|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 24 / 394 (6.09%) 33 | 9 / 259 (3.47%) 9 | |
| Rash macular subjects affected / exposed occurrences (all) | 24 / 394 (6.09%) 33 | 8 / 259 (3.09%) 12 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 31 / 394 (7.87%) 34 | 12 / 259 (4.63%) 16 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 105 / 394 (26.65%) 174 | 43 / 259 (16.60%) 63 | |
| Back pain subjects affected / exposed occurrences (all) | 77 / 394 (19.54%) 103 | 47 / 259 (18.15%) 57 | |
| Bone pain subjects affected / exposed occurrences (all) | 37 / 394 (9.39%) 47 | 19 / 259 (7.34%) 21 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 35 / 394 (8.88%) 47 | 21 / 259 (8.11%) 25 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 20 / 394 (5.08%) 23 | 15 / 259 (5.79%) 18 | |
| Myalgia subjects affected / exposed occurrences (all) | 22 / 394 (5.58%) 29 | 14 / 259 (5.41%) 15 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 32 / 394 (8.12%) 41 | 26 / 259 (10.04%) 31 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 91 / 394 (23.10%) 161 | 69 / 259 (26.64%) 125 | |
| Bronchitis | | | |

| | | | |
|------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed | 40 / 394 (10.15%) | 19 / 259 (7.34%) | |
| occurrences (all) | 55 | 23 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 28 / 394 (7.11%) | 10 / 259 (3.86%) | |
| occurrences (all) | 34 | 12 | |
| Herpes zoster | | | |
| subjects affected / exposed | 37 / 394 (9.39%) | 14 / 259 (5.41%) | |
| occurrences (all) | 38 | 16 | |
| Influenza | | | |
| subjects affected / exposed | 38 / 394 (9.64%) | 29 / 259 (11.20%) | |
| occurrences (all) | 42 | 32 | |
| Sinusitis | | | |
| subjects affected / exposed | 20 / 394 (5.08%) | 6 / 259 (2.32%) | |
| occurrences (all) | 29 | 8 | |
| Pneumonia | | | |
| subjects affected / exposed | 24 / 394 (6.09%) | 15 / 259 (5.79%) | |
| occurrences (all) | 31 | 16 | |
| Pharyngitis | | | |
| subjects affected / exposed | 20 / 394 (5.08%) | 9 / 259 (3.47%) | |
| occurrences (all) | 21 | 13 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 100 / 394 (25.38%) | 54 / 259 (20.85%) | |
| occurrences (all) | 187 | 89 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 21 / 394 (5.33%) | 17 / 259 (6.56%) | |
| occurrences (all) | 26 | 19 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 27 February 2019 | The following changes were made as per Amendment 3: 1. Added 3 interim analysis (IAs) for OS—at approximately 140 OS events, 170 OS events, and 230 OS events. 2. Updated details of the already completed PFS analysis (first IA) to align with the statistical analysis plan (SAP). |
| 21 November 2021 | The following changes were made as per Amendment 4: 1. Created Streamlined Schedule of Events to show only the assessments needed now that all participants are in follow-up, essentially replacing the original Schedule of Events. 2. Removed investigator assessment of disease response/status. 3. Added information about alternative monitoring approaches in the event a monitor cannot visit the site in a timely manner due to the coronavirus disease 2019 (COVID-19) pandemic. 3. Added death as a reason for a participant's withdrawal from the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not specified

Notes: