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/m^2]) 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	58.2	56.8	
standard deviation	± 7.92	± 8.17	-
Gender categorical Units: Subjects			
Male	162	252	414
Female	99	143	242
Ethinicity 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	
Ethinicity 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 ≥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 ≥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 ≥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 ≥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 (± 1.9842)			
Cycle 8 Day 1 (n=338)	2.637 (± 1.7074)			
Cycle 9 Day 1 (n=327)	2.610 (± 1.9380)			
Cycle 10 Day 1 (n=321)	2.594 (± 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 (± 1.57)	-4.1 (± 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

End point title	Time to Improvement of PN Events

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.

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%)	130.0 (36.0 to 520.0)	134.0 (70.0 to 252.0)		

Statistical analyses

No statistical analyses for this end point

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

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 AEs were not dose escalated.

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 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			

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			

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	

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			

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	

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	

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			

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			

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	

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			

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	

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

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

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