Clinical trial results:
An Open-label, Multicenter, Phase 2 Study of Oral IXAZOMIB (MLN9708) in Adult Patients With Relapsed and/or Refractory Follicular Lymphoma

Summary

EudraCT number	2013-002302-32
Trial protocol	BE GB IT ES
Global end of trial date	23 March 2017

Results information

Result version number	v1
This version publication date	05 April 2018
First version publication date	05 April 2018

Trial information

Trial identification

Sponsor protocol code	C16017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01939899
WHO universal trial number (UTN)	U1111-1164-7551

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Medical Director, Clinical Science, Millennium Pharmaceuticals, Inc., 001 8778253327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Millennium Pharmaceuticals, Inc., 001 8778253327, 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	23 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the anti-tumor activity of oral Ixazomib as measured by overall response rate (ORR) in adult subjects with relapsed and/or refractory follicular lymphoma (FL).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	29
EEA total number of subjects	20

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)	11
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 11 investigative sites in the United States, Belgium, Canada, United Kingdom and Italy from 31 October 2013 to 23 March 2017.

Pre-assignment

Screening details:

Subjects with follicular lymphoma (FL) prior to treatment were enrolled in this 2 phase study: Lead in dose finding phase in which maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of ixazomib was evaluated and Phase 2 proteasome subunit beta type-1 (PSMB1) was done to evaluate the safety, efficacy, tolerability of ixazomib.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lead-in Dose Finding Phase: Ixazomib 4 mg

Arm description:

Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in non-hodgkin lymphoma (NHL) subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg

Arm description:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg

Arm description:

Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days

treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm title	Phase 2: PSMB1 Positive

Arm description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in relapsed Or refractory follicular lymphoma (RRFL) subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Arm title	Phase 2: PSMB1 Negative

Arm description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Number of subjects in period 1	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Started	3	7	6
Completed	3	7	6

Number of subjects in period 1	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative

Started	12	1
Completed	12	1

Period 2

Period 2 title	Lead-in Dose Finding Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lead-in Dose Finding Phase: Ixazomib 4 mg

Arm description:

Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in non-hodgkin lymphoma (NHL) subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg

Arm description:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg

Arm description:

Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Number of subjects in period 2[1]	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Started	3	7	6
Completed	1	0	1
Not completed	2	7	5
Adverse event, serious fatal	-	3	1
Other	-	-	1
Disease Progression	2	4	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The subjects in the preceding period were evaluated for baseline characteristics. The subjects then started the lead in dose finding period.

Period 3

Period 3 title	Phase 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Phase 2: PSMB1 Positive

Arm description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Arm title	Phase 2: PSMB1 Negative

Arm description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Number of subjects in period 3	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative
Started	12	1
Completed	1	0
Not completed	11	1
Consent withdrawn by subject	2	-
Disease Progression	9	1

Baseline characteristics

Reporting groups	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 4 mg
Reporting group description:	
Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in non-hodgkin lymphoma (NHL) subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg
Reporting group description:	
Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Reporting group description:	
Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Phase 2: PSMB1 Positive
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in relapsed Or refractory follicular lymphoma (RRFL) subjects.	
Reporting group title	Phase 2: PSMB1 Negative
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.	

Reporting group values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Number of subjects	3	7	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	4	3
From 65-84 years	3	3	3
85 years and over	0	0	0
Age Continuous			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: years			
arithmetic mean	72.0	57.9	64.3
standard deviation	± 6.56	± 11.13	± 7.71

Sex: Female, Male Units: Subjects			
Female	1	1	1
Male	2	6	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	7	6
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Belgium|	1	2	3
Canada|	0	1	2
United Kingdom|	0	3	1
Italy|	0	0	0
United States|	2	1	0
Smoking classification Units: Subjects			
Never smoked	2	4	5
Current smoker	0	2	0
Ex-smoker	1	1	1
Height			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: centimeter (cm)			
arithmetic mean	170.0	175.0	169.2
standard deviation	± 7.04	± 11.50	± 9.11
Weight			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: kilogram (kg)			
arithmetic mean	76.1	85.8	85.3
standard deviation	± 11.27	± 20.72	± 10.95

Reporting group values	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative	Total
Number of subjects	12	1	29
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	0	11
From 65-84 years	8	1	18
85 years and over	0	0	0

Age Continuous			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: years			
arithmetic mean	64.7	79.0	
standard deviation	± 11.73	± 99999	-
Sex: Female, Male			
Units: Subjects			
Female	4	1	8
Male	8	0	21
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	12	0	28
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Region of Enrollment			
Units: Subjects			
Belgium|	3	0	9
Canada|	0	0	3
United Kingdom|	2	0	6
Italy|	5	0	5
United States|	2	1	6
Smoking classification			
Units: Subjects			
Never smoked	7	1	19
Current smoker	0	0	2
Ex-smoker	5	0	8
Height			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: centimeter (cm)			
arithmetic mean	168.8	157.5	
standard deviation	± 6.70	± 99999	-
Weight			
Here, 99999 in the standard deviation signifies not estimable since only 1 subject was analyzed.			
Units: kilogram (kg)			
arithmetic mean	78.7	82.4	
standard deviation	± 13.54	± 99999	-

End points

End points reporting groups

Reporting group title	Lead-in Dose Finding Phase: Ixazomib 4 mg
Reporting group description:	
Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in non-hodgkin lymphoma (NHL) subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg
Reporting group description:	
Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Reporting group description:	
Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Phase 2: PSMB1 Positive
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in relapsed Or refractory follicular lymphoma (RRFL) subjects.	
Reporting group title	Phase 2: PSMB1 Negative
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 4 mg
Reporting group description:	
Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in non-hodgkin lymphoma (NHL) subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg
Reporting group description:	
Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Reporting group description:	
Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.	
Reporting group title	Phase 2: PSMB1 Positive
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.	
Reporting group title	Phase 2: PSMB1 Negative
Reporting group description:	
Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.	
Subject analysis set title	All Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Subject analysis set title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg (RP2D)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Subject analysis set title	Phase 2: PSMB1 Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Subject analysis set title	Phase 2: PSMB1 Negative
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Primary: Number of Subjects with Overall Response Rate (ORR)

End point title	Number of Subjects with Overall Response Rate (ORR)[1]

End point description:

ORR is defined as the percentage of subjects with complete response (CR) or partial response (PR) as assessed by the investigator using the international Working Group criteria for subjects CR: disappearance of all target lesions, non-target lesions, no new lesions, and normalization of tumor marker level. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, no progression in non-target lesion, and no new lesions. The response-evaluable population included all subjecs who received at least 1 dose of ixazomib, had measurable disease at baseline, and had at least 1 post baseline disease assessment.

End point type	Primary

End point timeframe:

Baseline up to Day 15 Cycle 29 (approximately up to Day 802) or until PD or the start of alternate therapies

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	Phase 2: PSMB1 Positive
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	5	5	12
Units: subjects				
CR|	0	0	0	0
PR|	0	0	0	1
Stable Disease (SD)|	1	2	2	4
PD|	2	3	3	7

End point values	Phase 2: PSMB1 Negative			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: subjects				
CR|	0			
PR|	0			
Stable Disease (SD)|	0			
PD|	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Lead-in Dose Finding Phase: Recommended Phase 2 Dose (RP2D)

End point title	Lead-in Dose Finding Phase: Recommended Phase 2 Dose (RP2D)

End point description:

The dose limiting toxicity (DLT)- evaluable population included all subjects who received all Cycle 1 doses of ixazomib and had completed Cycle 1 safety procedures, or experience a DLT in Cycle 1 in the lead-in dose finding phase of the study.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 1 Day 28

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: mg				
number (not applicable)	5.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from the date of the first dose of study treatment to the date of first documented PD or death. Subjects without documentation of PD will be censored at the date of last response assessment that is SD or better. Subjects without response assessment will be censored at the date of the first dose. The modified intent-to-treat (mITT) population included all subjects who received at least 1 dose of ixazomib in the phase 2 portion of the study or who received at least 1 dose of ixazomib and are treated at the RP2D in the lead-in dose finding phase of the study. Here, 99999 in the confidence interval signifies not estimable since only 1 subject was analyzed.

End point type	Secondary

End point timeframe:

Time from the date of first dose of study treatment to the date of first documented PD or death (approximately up to Day 802)

End point values	Lead-in Dose Finding Phase: Ixazomib 5.3 mg (RP2D)	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	12	1	
Units: months				
median (confidence interval 95%)	1.9 (1.68 to 3.71)	2.4 (1.87 to 11.50)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Rate of Disease Control

End point title	Phase 2: Rate of Disease Control

End point description:

Rate of disease control is defined as percentage of subjects who achieved a SD or better for greater than or equal to (>=) 6 months. The response-evaluable population included all subjects who received at least 1 dose of ixazomib, had measurable disease at baseline, and had at least 1 post baseline disease assessment. Here, 99999 signifies not estimable since only 1 subject was analyzed.

End point type	Secondary

End point timeframe:

Baseline or until occurrence of disease progression, unacceptable toxicities, or discontinuation of study due to any other reasons (approximately up to Day 805)

End point values	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	1		
Units: percentage of subjects				
number (confidence interval 95%)	16.7 (2.09 to 48.41)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR is defined as the time from the date of the first dose of study treatment to the date of the first documentation of a PR or better response in a subject who responded. The response-evaluable population included all subjects who received at least 1 dose of ixazomib, had measurable disease at baseline, and had at least 1 post baseline disease assessment. Here, 99999 in the data signifies not estimable since low number of subjects with CR and PR.

End point type	Secondary

End point timeframe:

Time from the date of first dose of study treatment to the date of first documented PD or death (approximately up to Day 802)

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	Phase 2: PSMB1 Positive
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	5	5	12
Units: months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

End point values	Phase 2: PSMB1 Negative			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: months				
median (full range (min-max))	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The DOR is defined as the time from the date of first documentation of a response to the date of first documented PD. Responders without documentation of PD will be censored at the date of last response assessment. DOR will be categorized as CR+PR and CR. The response-evaluable population included all subjects who received at least 1 dose of ixazomib, had measurable disease at baseline, and had at least 1 post baseline disease assessment. Here, 99999 in the data signifies not estimable since low number of subjects with CR and PR.

End point type	Secondary

End point timeframe:

Time from the date of first documentation of a response to the date of first documented PD (approximately up to Day 802)

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	Phase 2: PSMB1 Positive
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	7	6	12
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

End point values	Phase 2: PSMB1 Negative			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Subjects with Response Rates in PSMB1 Positive and PSMB1 Negative

End point title	Phase 2: Number of Subjects with Response Rates in PSMB1 Positive and PSMB1 Negative

End point description:

The biomarker population included all subjects positive or negative for the PSMB1 biomarker and where the assay has passed quality control. Data will be derived from a baseline blood sample.

End point type	Secondary

End point timeframe:

Baseline up to occurrence of disease progression, unacceptable toxicities, or discontinuation of study due to any other reasons (approximately up to Day 802)

End point values	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	1		
Units: subjects	12	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing 1 or More Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects Experiencing 1 or More Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

The safety population included all enrolled subjects who had received at least 1 dose of ixazomib.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study drug (approximately up to Day 832)

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	Phase 2: PSMB1 Positive
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	7	6	12
Units: subjects				
TEAE|	3	7	6	11
SAE|	1	3	4	4

End point values	Phase 2: PSMB1 Negative			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: subjects				
TEAE|	1			
SAE|	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Lead-in Dose Finding Phase: Cmax: Maximum Observed Plasma

Concentration for Ixazomib

End point title	Lead-in Dose Finding Phase: Cmax: Maximum Observed Plasma Concentration for Ixazomib

End point description:

The plasma pharmacokinetic (PK) analysis population included all subjects enrolled in the lead-in dose finding phase that had sufficient dosing data and ixazomib concentration-time data. The PK analysis population where data at specified time points was available.

End point type	Secondary

End point timeframe:

Cycle 1, Days 1 and 15 pre-dose and at multiple time points (up to 168 hours) post-dose

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	6	
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1|	141.3333 (± 52.27173)	103.4717 (± 57.53181)	121.1167 (± 69.07212)	
Cycle 1 Day 15|	124.2667 (± 71.01840)	144.0667 (± 105.15884)	152.0667 (± 102.71131)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lead-in Dose Finding Phase: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib

End point title	Lead-in Dose Finding Phase: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Ixazomib

End point description:

The plasma PK analysis population included all subjects enrolled in the lead-in dose finding phase that had sufficient dosing data and ixazomib concentration-time data. The PK analysis population where data at specified time points was available.

End point type	Secondary

End point timeframe:

Cycle 1, Days 1 and 15 pre-dose and at multiple time points (up to 168 hours) post-dose

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	6	
Units: hour				
median (full range (min-max))				

Cycle 1 Day 1|	1.0000 (0.500 to 1.500)	1.0000 (0.500 to 1.500)	1.0500 (1.000 to 3.750)	
Cycle 1 Day 15|	1.0000 (0.500 to 2.000)	0.7500 (0.467 to 1.520)	1.0000 (0.500 to 1.500)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lead-in Dose Finding Phase: AUC(0-168): Area Under the Plasma Concentration-time Curve from Time 0 to 168 Hours Postdose for Ixazomib

End point title	Lead-in Dose Finding Phase: AUC(0-168): Area Under the Plasma Concentration-time Curve from Time 0 to 168 Hours Postdose for Ixazomib

End point description:

The PK analysis set where Cycle 1 Day 1 and 15 assessment were available. The PK analysis population included all subjects enrolled in the lead-in dose finding phase that had sufficient dosing data and ixazomib concentration-time data. The PK analysis population where data at specified time points was available.

End point type	Secondary

End point timeframe:

Cycle 1, Days 1 and 15 pre-dose and at multiple time points (up to 168 hours) post-dose

End point values	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	6	
Units: hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1|	1265.0000 (± 332.34019)	1030.1429 (± 367.90326)	1680.3333 (± 656.01240)	
Cycle 1 Day 15|	2440.0000 (± 272.21315)	2007.0000 (± 986.30117)	3120.0000 (± 2503.83706)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of study drug and no more than 30 days after the last dose of study drug (up to Cycle 29)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Lead-in Dose Finding Phase: Ixazomib 4 mg

Reporting group description:

Ixazomib 4 milligram (mg), solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or progressive disease (PD) or the start of alternate therapies during lead-in dose finding in NHL subjects.

Reporting group title	Lead-in Dose Finding Phase: Ixazomib 5.3 mg

Reporting group description:

Ixazomib 5.3 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Reporting group title	Lead-in Dose Finding Phase: Ixazomib 7.0 mg

Reporting group description:

Ixazomib 7 mg, solution, orally, once on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during lead-in dose finding in NHL subjects.

Reporting group title	Phase 2: PSMB1 Positive

Reporting group description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Reporting group title	Phase 2: PSMB1 Negative

Reporting group description:

Ixazomib RP2D mg, solution, orally, once weekly on Day 1, 8, and 15 followed by 13 days of rest in a 28-days treatment cycle for a maximum of 29 cycles, or PD or the start of alternate therapies during phase 2 finding in RRFL subjects.

Serious adverse events	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	3 / 7 (42.86%)	4 / 6 (66.67%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Herpes zoster			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	1 / 1 (100.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			

subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (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 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lead-in Dose Finding Phase: Ixazomib 4 mg	Lead-in Dose Finding Phase: Ixazomib 5.3 mg	Lead-in Dose Finding Phase: Ixazomib 7.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	7 / 7 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Orthostatic hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	4 / 7 (57.14%)	3 / 6 (50.00%)
occurrences (all)	1	5	3
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Chills			

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Neuropathy peripheral			

subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	1	1	4
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	3 / 6 (50.00%)
occurrences (all)	2	0	3
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 3 (66.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	4 / 7 (57.14%)	6 / 6 (100.00%)
occurrences (all)	1	4	10
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	3 / 7 (42.86%)	3 / 6 (50.00%)
occurrences (all)	5	4	7
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	1 / 7 (14.29%)	4 / 6 (66.67%)
occurrences (all)	3	1	10
Abdominal pain			
subjects affected / exposed	3 / 3 (100.00%)	0 / 7 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	2
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haemorrhoids			

subjects affected / exposed	2 / 3 (66.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 3 (100.00%)	2 / 7 (28.57%)	3 / 6 (50.00%)
occurrences (all)	3	2	3
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase 2: PSMB1 Positive	Phase 2: PSMB1 Negative	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	1 / 1 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Asthenia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	6	0	
Pyrexia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	11	0	
Oedema peripheral			

subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	5	0	
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 12 (41.67%)	1 / 1 (100.00%)	
occurrences (all)	17	1	
Nausea			
subjects affected / exposed	5 / 12 (41.67%)	1 / 1 (100.00%)	
occurrences (all)	11	1	
Vomiting			
subjects affected / exposed	5 / 12 (41.67%)	1 / 1 (100.00%)	
occurrences (all)	16	1	
Abdominal pain			
subjects affected / exposed	3 / 12 (25.00%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Abdominal pain upper			

subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 1 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			

subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 12 (16.67%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported