Clinical trial results:
A Multicenter, Randomized, Open-label Phase 2 Study Evaluating the Safety and Efficacy of Three Different Regimens of Oral Panobinostat in Combination with Subcutaneous Bortezomib and Oral Dexamethasone in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma Who Have Been Previously Exposed to Immunomodulatory Agents

Summary

EudraCT number	2015-001564-19
Trial protocol	ES BE SE NO DE NL HU GR PL CZ PT IT FR
Global end of trial date	15 August 2022

Results information

Result version number	v1 (current)
This version publication date	13 September 2024
First version publication date	13 September 2024

Trial information

Trial identification

Sponsor protocol code	CLBH589D2222

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02654990
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	pharmaand GmbH
Sponsor organisation address	Taborstraße 1, Wien, Austria, 1020
Public contact	Medical Information Department, pharmaand GmbH, +43 13560006, medinfo@pharmaand.com
Scientific contact	Medical Information Department, pharmaand GmbH, +43 13560006, medinfo@pharmaand.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	15 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study data was transferred to zr pharma& following the divestment of panobinostat to pharma&. Prior to study completion under the sponsorship of Secura Bio, the study was initiated and conducted in part under the sponsorship of Novartis.

The primary objective of the study was to estimate the overall response rate (ORR) of each of 3 treatment regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone during up to 8 cycles of therapy, according to the International Myeloma Working Group 2014 (IMWG) criteria, as assessed by an Independent Review Committee (IRC).

Protection of trial subjects:

The study was performed in compliance with the Declaration of Helsinki, the International Council on Harmonisation Guidelines for Good Clinical Practice, and regulatory requirements as applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Lebanon: 14
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Thailand: 20
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Belgium: 1

Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	351
EEA total number of subjects	224

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)	152
From 65 to 84 years	196
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Once randomized, participants were included in the post-treatment follow-up for efficacy until disease progression, death, loss to follow-up or withdrawal of consent, and, thereafter, in the survival follow-up even if they did not receive a dose of study treatment, as applicable.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - Panobinostat (20 mg, TIW)

Arm description:

Participants received 20 milligrams (mg) panobinostat thrice a week (TIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	PAN, LBH589, Farydak
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Panobinostat (20 mg) TIW, 2 weeks on/1 week off in combination with bortezomib and dexamethasone.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	BTZ, Velcade
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/metre squared (m^2) subcutaneous administration; Cycle 1-4: 2 weeks on/1 week off twice a week for participants ≤75 years at time of screening; once a week for participant >75 years Cycle 5+: once a week for all participants.

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

Dosage and administration details:

Pre- and 24 h after BTZ administration; participants ≤75 years at time of screening: 20 mg/dose participants >75 years: 10 mg/dose.

Arm title	Arm B - Panobinostat (20 mg, BIW)

Arm description:

Participants received 20 mg panobinostat twice a week (BIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.

Arm type	Experimental

Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	PAN, LBH589, Farydak
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Panobinostat (20 mg) TIW, 2 weeks on/1 week off in combination with bortezomib and dexamethasone.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	BTZ, Velcade
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m^2 subcutaneous administration; Cycle 1-4: 2 weeks on/1 week off twice a week for participants ≤75 years at time of screening; once a week for participant >75 years Cycle 5+: once a week for all participants.

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

Dosage and administration details:

Pre- and 24 h after BTZ administration; participants ≤75 years at time of screening: 20 mg/dose participants >75 years: 10 mg/dose.

Arm title	Arm C - Panobinostat (10 mg, TIW)

Arm description:

Participants received 10 mg panobinostat TIW, 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	PAN, LBH589, Farydak
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Panobinostat (20 mg) TIW, 2 weeks on/1 week off in combination with bortezomib and dexamethasone.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	BTZ, Velcade
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m^2 subcutaneous administration; Cycle 1-4: 2 weeks on/1 week off twice a week for participants ≤75 years at time of screening; once a week for participant >75 years Cycle 5+: once a week for all participants.

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

Dosage and administration details:

Pre- and 24 h after BTZ administration; participants ≤75 years at time of screening: 20 mg/dose participants >75 years: 10 mg/dose.

Number of subjects in period 1[1]	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)
Started	82	83	83
Received at Least 1 Dose of Study Drug	79 [2]	82 [3]	80 [4]
Completed	82	83	83

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of participants reported in the baseline period comprise the full analysis set (FAS): all participants to whom study treatment was assigned by randomization.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants reported in this milestone comprise the Safety Set: all participants who received any study treatment.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants reported in this milestone comprise the Safety Set: all participants who received any study treatment.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of participants reported in this milestone comprise the Safety Set: all participants who received any study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - Panobinostat (20 mg, TIW)
Reporting group description:	
Participants received 20 milligrams (mg) panobinostat thrice a week (TIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	
Reporting group title	Arm B - Panobinostat (20 mg, BIW)
Reporting group description:	
Participants received 20 mg panobinostat twice a week (BIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	
Reporting group title	Arm C - Panobinostat (10 mg, TIW)
Reporting group description:	
Participants received 10 mg panobinostat TIW, 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	

Reporting group values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)
Number of subjects	82	83	83
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)	32	39	40
From 65-84 years	50	43	43
85 years and over	0	1	0
Age continuous Units: years			
median	67.0	65.0	66.0
full range (min-max)	45 to 83	47 to 87	33 to 84
Gender categorical Units: Subjects			
Female	40	39	33
Male	42	44	50
Race Units: Subjects			
Asian	6	7	10
American Indian or Alaska Native	1	0	0
Black or African American	1	0	2
White	73	72	68
Other	1	4	3
Ethnicity Units: Subjects			
Hispanic or Latino	4	5	9

Not Hispanic or Latino	49	43	38
Unknown/Not Reported	8	8	4
Southeast Asian	4	4	6
Other	17	23	26
Eastern Cooperative Oncology Group Performance Status			
Scale to assess disease progression and disease effects on daily living abilities, as well as determine appropriate treatment and prognosis. Status range includes: 0 (fully active); 1 (restricted physical activity); 2 (unable to carry out work activities); 3 (limited self-care); 4 (completely disabled).			
Units: Subjects			
Status - 0	38	38	42
Status - 1	36	45	35
Status - 2	8	0	6
Status - 3	0	0	0
Status - 4	0	0	0

Reporting group values	Total		
Number of subjects	248		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	111		
From 65-84 years	136		
85 years and over	1		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	112		
Male	136		
Race			
Units: Subjects			
Asian	23		
American Indian or Alaska Native	1		
Black or African American	3		
White	213		
Other	8		
Ethnicity			
Units: Subjects			
Hispanic or Latino	18		
Not Hispanic or Latino	130		
Unknown/Not Reported	20		
Southeast Asian	14		
Other	66		

Eastern Cooperative Oncology Group Performance Status			
Scale to assess disease progression and disease effects on daily living abilities, as well as determine appropriate treatment and prognosis. Status range includes: 0 (fully active); 1 (restricted physical activity); 2 (unable to carry out work activities); 3 (limited self-care); 4 (completely disabled).			
Units: Subjects			
Status - 0	118		
Status - 1	116		
Status - 2	14		
Status - 3	0		
Status - 4	0		

End points

End points reporting groups

Reporting group title	Arm A - Panobinostat (20 mg, TIW)
Reporting group description:	
Participants received 20 milligrams (mg) panobinostat thrice a week (TIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	
Reporting group title	Arm B - Panobinostat (20 mg, BIW)
Reporting group description:	
Participants received 20 mg panobinostat twice a week (BIW), 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	
Reporting group title	Arm C - Panobinostat (10 mg, TIW)
Reporting group description:	
Participants received 10 mg panobinostat TIW, 2 weeks on/1 week off in combination with subcutaneous bortezomib and oral dexamethasone.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants to whom study treatment was assigned by randomization.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received any study treatment.	
Subject analysis set title	Pharmacokinetics Analysis Set (PAS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants with at least 1 evaluable pharmacokinetics concentration of panobinostat after dosing on Day 1.	

Primary: ORR

End point title	ORR[1]
End point description:	
ORR is defined as the percentage of participants with a confirmed partial response (PR) or better (immunophenotypic complete response [iCR] or stringent complete response [sCR] or complete response [CR] or very good partial response [VGPR]) as their best overall response after completion of up to 8 cycles of assigned study regimen. Each cycle was 21 days long. Best overall response was the best post-baseline confirmed overall response observed in a given participant and was determined based on overall responses observed at all post-baseline response assessments, recorded from randomization until progressive disease (PD), death, start of new therapy, withdrawal of consent, or end of study, whatever came first. ORR was assessed blindly per IRC according to IMWG criteria.	
End point type	Primary
End point timeframe:	
Up to 168 days	

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 statistics (percentage of participants plus confidence interval) are reported for this primary end point, as prespecified in the statistical analysis plan.

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[2]	83[3]	83[4]	
Units: Percentage of Participants				
number (confidence interval 95%)	62.2 (50.8 to 72.7)	65.1 (53.8 to 75.2)	50.6 (39.4 to 61.8)	

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: ORR Throughout the Study

End point title	ORR Throughout the Study

End point description:

ORR is defined as the percentage of participants with a confirmed PR or better (iCR or sCR or CR or VGPR) as their best overall response throughout the entire study. Best overall response was the best post-baseline confirmed overall response observed in a given participant and was determined based on overall responses observed at all post-baseline response assessments, recorded from randomization until PD, death, start of new therapy, withdrawal of consent or end of study, whatever came first. ORR was assessed blindly per IRC according to IMWG criteria.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[5]	83[6]	83[7]	
Units: Percentage of Participants				
number (confidence interval 95%)	62.2 (50.8 to 72.7)	67.5 (56.3 to 77.4)	53.0 (41.7 to 64.1)	

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: iCR Rate

End point title	iCR Rate

End point description:

iCR, based on IMWG criteria per blinded IRC assessment, is defined as: negative immunofixation of serum and urine; disappearance of any soft tissue plasmacytoma(s), in the case of any presence of soft tissue plasmacytoma(s) at baseline; less than 5% plasma cells in bone marrow; normal free light chain

(FLC) ratio; absence of clonal plasma cells in bone marrow analysed by immunohistochemistry or 2- to 4-color flow cytometry; absence of phenotypically aberrant plasma cells (clonal) in bone marrow (BM) with a minimum of 1 million total BM cells analysed by multiparametric flow cytometry (>4 colours). Results reported as percentage of participants achieving iCR.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[8]	83[9]	83[10]	
Units: Percentage of Participants				
number (not applicable)	3.7	1.2	1.2	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: sCR Rate

End point title	sCR Rate

End point description:

sCR, based on IMWG criteria per blinded IRC assessment, is defined as: negative immunofixation of serum and urine; disappearance of any soft tissue plasmacytoma(s), in the case of any presence of soft tissue plasmacytoma(s) at baseline; less than 5% plasma cells in bone marrow; normal FLC ratio; absence of clonal plasma cells in bone marrow analysed by immunohistochemistry or 2- to 4-colour flow cytometry. Results reported as percentage of participants achieving sCR.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[11]	83[12]	83[13]	
Units: Percentage of Participants				
number (not applicable)	1.2	1.2	3.6	

Notes:

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: CR Rate

End point title	CR Rate

End point description:

CR, based on IMWG criteria per blinded IRC assessment, is defined as: negative immunofixation of serum and urine; disappearance of any soft tissue plasmacytoma(s), in the case of any presence of soft tissue plasmacytoma(s) at baseline; less than 5% plasma cells in bone marrow; in case the only measurable disease at baseline is the serum FLC assessment, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR. Results reported as percentage of participants achieving CR.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[14]	83[15]	83[16]	
Units: Percentage of Participants				
number (not applicable)	8.5	8.4	2.4	

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: VGPR Rate

End point title	VGPR Rate

End point description:

VGPR, based on IMWG criteria per blinded IRC assessment, is defined as: serum and/or urine M protein detectable by immunofixation but not on protein electrophoresis, or ≥90% reduction from baseline in serum) and urine M protein <100 mg/24 hours); in the case of the presence of any soft tissue plasmacytoma(s) at baseline, a reduction in the sum of the products of the cross-diameters by ≥50% from baseline is required; in case the only measurable disease in a participant at baseline is the serum FLC level (that is, no measurable disease in serum and urine protein electrophoresis), a decrease of >90% in the difference between involved and uninvolved FLC levels from baseline is required. Results reported as percentage of participants achieving VGPR.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[17]	83[18]	83[19]	
Units: Percentage of Participants				
number (not applicable)	19.5	25.3	20.5	

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

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, assessed based on IMWG criteria per blind IRC assessment, is defined as the time from date of randomization to date of first documented disease progression or death (regardless of cause of death).

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[20]	83[21]	83[22]	
Units: Months				
median (confidence interval 95%)	15 (7.4 to 24.7)	13 (7.0 to 13.8)	8 (5.0 to 10.7)	

Notes:

[20] - FAS

[21] - FAS

[22] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from date of randomization to the date of death due to any cause. '9999' = Not evaluable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[23]	83[24]	83[25]	
Units: Months				
median (confidence interval 95%)	35 (27.8 to 9999)	32 (30.7 to 9999)	22 (18.6 to 9999)	

Notes:

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax): Panobinostat

End point title	Maximum Plasma Concentration (Cmax): Panobinostat

End point description:

Serial blood samples were collected for panobinostat Cmax analysis. Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed. Results are reported in nanograms/millilitre (ng/mL).

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Pre-dose, up to 8 hours post dose)

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50[26]	64[27]	62[28]	
Units: ng/mL				
arithmetic mean (standard deviation)	14.30 (± 7.77)	14.12 (± 8.96)	6.13 (± 3.51)	

Notes:

[26] - PAS

[27] - PAS

[28] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Bortezomib

End point title	Cmax: Bortezomib

End point description:

Serial blood samples were collected for bortezomib Cmax analysis. Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed. Results are reported in ng/mL.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Pre-dose, up to 8 hours post dose)

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[29]	69[30]	63[31]	
Units: ng/mL				
arithmetic mean (standard deviation)	16.67 (± 7.79)	19.47 (± 10.00)	18.29 (± 8.80)	

Notes:

[29] - PAS

[30] - PAS

[31] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (Tmax): Panobinostat

End point title	Time to Reach Cmax (Tmax): Panobinostat

End point description:

Serial blood samples were collected for panobinostat Tmax analysis. Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed. Results are reported in hours.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Pre-dose, up to 8 hours post dose)

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50[32]	64[33]	62[34]	
Units: hour				
arithmetic mean (standard deviation)	1.93 (± 1.53)	1.80 (± 1.63)	1.82 (± 1.53)	

Notes:

[32] - PAS

[33] - PAS

[34] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Bortezomib

End point title	Tmax: Bortezomib

End point description:

Serial blood samples were collected for bortezomib Tmax analysis. Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed. Results are reported in hours.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Pre-dose, up to 8 hours post dose)

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[35]	69[36]	63[37]	
Units: Hour				
arithmetic mean (standard deviation)	0.84 (± 0.46)	0.77 (± 0.36)	0.77 (± 0.39)	

Notes:

[35] - PAS

[36] - PAS

[37] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure Response: Cmax for Panobinostat

End point title	Exposure Response: Cmax for Panobinostat

End point description:

The exposure-response relationship was assessed utilizing Cmax (Cycle 1 Day 1) for panobinostat versus the outcomes of ORR, grade 3/4 thrombocytopenia, and grade 3/4 diarrhoea. Two statistical models were used: logistic regression models, in which these 3 outcomes were treated in a binary fashion according to their occurrence; Cox regression models, with the relevant outcomes being the time to occurrence of grade 3/4 thrombocytopenia and the time to occurrence of grade 3/4 diarrhoea. Results are reported as model-based probability. An increase in the model-based probability indicates an increase in the occurrence of the outcomes (ORR, grade 3/4 thrombocytopenia, 3/4 diarrhoea) with increasing values of Cmax (that is, with increasing dose of panobinostat). Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed.

End point type	Secondary

End point timeframe:

Up to 5.2 Years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[38]	20[39]	18[40]	
Units: Percent Probability				
number (confidence interval 95%)				
ORR by IRC (up to 8 cycles)	63.1 (46.7 to 76.9)	62.2 (47.5 to 75.0)	35.3 (20.6 to 53.4)	
Grade 3/4 Thrombocytopenia	23.2 (17.7 to 51.2)	28.7 (17.5 to 43.4)	21.7 (10.6 to 39.4)	

Grade 3/4 Diarrhoea	6.2 (2.1 to 16.7)	7.5 (3.1 to 17.2)	2.5 (0.3 to 16.3)	

Notes:

[38] - FAS

[39] - FAS; ORR (N=19)

[40] - FAS; ORR (N=17); Thrombocytopenia (N=17)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Core 30-item Questionnaire (QLQ-C30) Global Health Status (GHS) Score

End point title	Change From Baseline in European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Core 30-item Questionnaire (QLQ-C30) Global Health Status (GHS) Score

End point description:

Health-related quality of life (HRQoL) was assessed by the EORTC QLQ-C30, which is frequently employed in clinical oncology trials and is recognized as reliable and valid. The EORTC QLQ-C30 measures functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact), and a GHS and quality-of-life scale. For each domain and item, a linear transformation is applied to standardize the score between 0 and 100. Results are presented specifically for the GHS score. A higher GHS score indicates a higher HRQoL. Each cycle was 21 days long. Here, 'Number of subjects analysed' refers to the number of evaluable participants analysed.

End point type	Secondary

End point timeframe:

Cycle 15 Day 1, at approximately 295 days

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[41]	16[42]	18[43]	
Units: Score on a Scale				
arithmetic mean (standard deviation)	6.0 (± 23.01)	0.0 (± 30.12)	-4.6 (± 24.12)	

Notes:

[41] - FAS

[42] - FAS

[43] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group- Neurotoxicity (GOG-Ntx) Neurotoxicity Subscale Score

End point title	Change From Baseline in the Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group- Neurotoxicity (GOG-Ntx) Neurotoxicity Subscale Score

End point description:

HRQoL was assessed by the FACT/GOG-Ntx, a 38-item questionnaire designed to assess general quality of life and severity and impact of neurotoxicity from systemic chemotherapy. It is frequently employed in clinical oncology trials and is recognized as a reliable and valid measure to assess symptoms associated with neurotoxicity. It focuses on 4 general quality of life domains for physical well-being, functional well-being, social/family well-being, and emotional well-being, and includes the neurotoxicity subscale domain to characterize treatment-related neurotoxicity. Results are presented specifically for the 11-item neurotoxicity subscale, which uses a 5-point rating scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). Each item is scored from 0-4, with the severity of neurotoxicity measured as the sum of the 11 items, ranging from 0 to 44. Lower scores indicate lower neurotoxicity and higher HRQoL. Each cycle was 21 days long.

End point type	Secondary

End point timeframe:

Cycle 15 Day 1, at approximately 295 days

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[44]	15[45]	18[46]	
Units: Score on a Scale				
arithmetic mean (standard deviation)	-3.6 (± 7.39)	-3.9 (± 4.19)	-0.1 (± 5.71)	

Notes:

[44] - FAS (Number of subjects analysed = the number of evaluable participants analysed)

[45] - FAS (Number of subjects analysed = the number of evaluable participants analysed)

[46] - FAS (Number of subjects analysed = the number of evaluable participants analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP, based on IMWG criteria per blinded IRC assessment, is defined as the time from the date of randomization to the date of the first documented disease progression or death due to multiple myeloma. '9999' = Not evaluable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[47]	83[48]	83[49]	
Units: Months				
median (confidence interval 95%)	17 (8.35 to 9999)	13 (7.0 to 16.1)	8 (5.9 to 11.6)	

Notes:

[47] - FAS

[48] - FAS

[49] - FAS

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, based on IMWG criteria per blinded IRC assessment, is the time between date of randomization to the date of first onset of PR or better response (iCR or sCR or CR or VGPR). '9999' = Not evaluable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[50]	83[51]	83[52]	
Units: Months				
median (confidence interval 95%)	3 (1 to 9999)	3 (1 to 9999)	3 (1 to 9999)	

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR, based on IMWG criteria per blinded IRC assessment, is defined as the duration from the first documented onset of PR or better (iCR or sCR or CR or VGPR) to the date of first documented disease progression or death due to multiple myeloma. '9999' = Not evaluable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 5.2 years

End point values	Arm A - Panobinostat (20 mg, TIW)	Arm B - Panobinostat (20 mg, BIW)	Arm C - Panobinostat (10 mg, TIW)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82[53]	83[54]	83[55]	
Units: month				
median (confidence interval 95%)	22 (13.9 to 9999)	12 (8.8 to 21.3)	10.429 (6.2 to 14.5)	

Notes:

[53] - FAS

[54] - FAS

[55] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed for 3 years. All-Cause Mortality was assessed from date of randomization until death, assessed up to 5.2 years.

Adverse event reporting additional description:

Safety Set: all participants who received any study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Arm A - Panobinostat (20 mg) TIW

Reporting group description:

Participants received panobinostat (20 mg) TIW with bortezomib and dexamethasone.

Reporting group title	Arm B - Panobinostat (20 mg) BIW

Reporting group description:

Participants received panobinostat (20 mg) BIW with bortezomib and dexamethasone.

Reporting group title	Arm C - Panobinostat (10 mg) TIW

Reporting group description:

Participants received panobinostat (10 mg) TIW with bortezomib and dexamethasone.

Serious adverse events	Arm A - Panobinostat (20 mg) TIW	Arm B - Panobinostat (20 mg) BIW	Arm C - Panobinostat (10 mg) TIW
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 78 (56.41%)	40 / 83 (48.19%)	36 / 80 (45.00%)
number of deaths (all causes)	34	41	47
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Haematological malignancy			

subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypotension			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 78 (0.00%)	3 / 83 (3.61%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Pyrexia			
subjects affected / exposed	0 / 78 (0.00%)	4 / 83 (4.82%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed[1]	0 / 39 (0.00%)	1 / 44 (2.27%)	0 / 48 (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
Orchitis noninfective			
subjects affected / exposed[2]	0 / 39 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Acute pulmonary oedema			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Pleural effusion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin C increased			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Subdural haematoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Transfusion-related acute lung injury			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Femoral neck fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Femur fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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

Spinal compression fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Cardiac arrest			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 2	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Methaemoglobinaemia			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	3 / 3	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal motility disorder			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Ileus			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Pancreatitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Cholelithiasis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Skin and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Arthralgia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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

Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 78 (10.26%)	11 / 83 (13.25%)	9 / 80 (11.25%)
occurrences causally related to treatment / all	4 / 8	7 / 14	4 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lower respiratory tract infection			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 78 (1.28%)	4 / 83 (4.82%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Diverticulitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus sepsis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Influenza			

subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Pneumonia viral			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Streptococcal sepsis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Upper respiratory tract infection			

subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	0 / 80 (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
Dehydration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Diabetic ketoacidosis			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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
Hypercalcaemia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	0 / 80 (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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event only affected male participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This adverse event only affected male participants.

Frequency threshold for reporting non-serious adverse events: 4.9 %

Non-serious adverse events	Arm A - Panobinostat (20 mg) TIW	Arm B - Panobinostat (20 mg) BIW	Arm C - Panobinostat (10 mg) TIW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 78 (100.00%)	82 / 83 (98.80%)	78 / 80 (97.50%)
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 78 (8.97%)	6 / 83 (7.23%)	1 / 80 (1.25%)
occurrences (all)	10	8	1
Hypertension			
subjects affected / exposed	6 / 78 (7.69%)	4 / 83 (4.82%)	5 / 80 (6.25%)
occurrences (all)	13	4	6
Orthostatic hypotension			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	5 / 80 (6.25%)
occurrences (all)	0	1	6

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 78 (34.62%)	25 / 83 (30.12%)	24 / 80 (30.00%)
occurrences (all)	66	54	43
Asthenia			
subjects affected / exposed	25 / 78 (32.05%)	29 / 83 (34.94%)	15 / 80 (18.75%)
occurrences (all)	57	56	24
Oedema peripheral			
subjects affected / exposed	23 / 78 (29.49%)	14 / 83 (16.87%)	14 / 80 (17.50%)
occurrences (all)	34	18	14
Pyrexia			
subjects affected / exposed	10 / 78 (12.82%)	12 / 83 (14.46%)	10 / 80 (12.50%)
occurrences (all)	15	16	13
Non-cardiac chest pain			
subjects affected / exposed	4 / 78 (5.13%)	3 / 83 (3.61%)	2 / 80 (2.50%)
occurrences (all)	4	3	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 78 (15.38%)	13 / 83 (15.66%)	16 / 80 (20.00%)
occurrences (all)	18	15	20
Dyspnoea			
subjects affected / exposed	11 / 78 (14.10%)	8 / 83 (9.64%)	8 / 80 (10.00%)
occurrences (all)	13	13	8
Epistaxis			
subjects affected / exposed	6 / 78 (7.69%)	4 / 83 (4.82%)	3 / 80 (3.75%)
occurrences (all)	7	5	3
Dysphonia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 83 (3.61%)	2 / 80 (2.50%)
occurrences (all)	4	4	2
Oropharyngeal pain			
subjects affected / exposed	4 / 78 (5.13%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences (all)	4	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 78 (8.97%)	20 / 83 (24.10%)	11 / 80 (13.75%)
occurrences (all)	12	28	15

Depression			
subjects affected / exposed	4 / 78 (5.13%)	1 / 83 (1.20%)	3 / 80 (3.75%)
occurrences (all)	4	1	3
Investigations			
Platelet count decreased			
subjects affected / exposed	11 / 78 (14.10%)	9 / 83 (10.84%)	6 / 80 (7.50%)
occurrences (all)	52	25	7
Blood creatine increased			
subjects affected / exposed	9 / 78 (11.54%)	7 / 83 (8.43%)	4 / 80 (5.00%)
occurrences (all)	29	18	6
Alanine aminotransferase increased			
subjects affected / exposed	8 / 78 (10.26%)	2 / 83 (2.41%)	2 / 80 (2.50%)
occurrences (all)	11	3	4
Weight decreased			
subjects affected / exposed	6 / 78 (7.69%)	5 / 83 (6.02%)	3 / 80 (3.75%)
occurrences (all)	8	6	3
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 78 (6.41%)	2 / 83 (2.41%)	0 / 80 (0.00%)
occurrences (all)	7	3	0
C-reactive protein increased			
subjects affected / exposed	4 / 78 (5.13%)	3 / 83 (3.61%)	1 / 80 (1.25%)
occurrences (all)	4	8	4
Neutrophil count decreased			
subjects affected / exposed	4 / 78 (5.13%)	0 / 83 (0.00%)	2 / 80 (2.50%)
occurrences (all)	12	0	3
White blood cell count decreased			
subjects affected / exposed	4 / 78 (5.13%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences (all)	11	0	0
Weight increased			
subjects affected / exposed	2 / 78 (2.56%)	6 / 83 (7.23%)	0 / 80 (0.00%)
occurrences (all)	2	6	0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	20 / 78 (25.64%)	22 / 83 (26.51%)	14 / 80 (17.50%)
occurrences (all)	39	35	26
Peripheral sensory neuropathy			

subjects affected / exposed	16 / 78 (20.51%)	9 / 83 (10.84%)	11 / 80 (13.75%)
occurrences (all)	35	23	21
Dizziness			
subjects affected / exposed	13 / 78 (16.67%)	12 / 83 (14.46%)	5 / 80 (6.25%)
occurrences (all)	17	18	5
Headache			
subjects affected / exposed	7 / 78 (8.97%)	6 / 83 (7.23%)	3 / 80 (3.75%)
occurrences (all)	10	6	3
Paraesthesia			
subjects affected / exposed	4 / 78 (5.13%)	5 / 83 (6.02%)	4 / 80 (5.00%)
occurrences (all)	7	6	5
Polyneuropathy			
subjects affected / exposed	3 / 78 (3.85%)	5 / 83 (6.02%)	5 / 80 (6.25%)
occurrences (all)	3	14	8
Dysgeusia			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	4 / 80 (5.00%)
occurrences (all)	2	3	7
Neuralgia			
subjects affected / exposed	0 / 78 (0.00%)	6 / 83 (7.23%)	0 / 80 (0.00%)
occurrences (all)	0	6	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	43 / 78 (55.13%)	37 / 83 (44.58%)	26 / 80 (32.50%)
occurrences (all)	140	122	126
Anaemia			
subjects affected / exposed	33 / 78 (42.31%)	22 / 83 (26.51%)	24 / 80 (30.00%)
occurrences (all)	83	58	74
Neutropenia			
subjects affected / exposed	25 / 78 (32.05%)	16 / 83 (19.28%)	10 / 80 (12.50%)
occurrences (all)	71	57	37
Leukopenia			
subjects affected / exposed	5 / 78 (6.41%)	1 / 83 (1.20%)	2 / 80 (2.50%)
occurrences (all)	12	4	2
Eye disorders			
Cataract			

subjects affected / exposed	6 / 78 (7.69%)	3 / 83 (3.61%)	1 / 80 (1.25%)
occurrences (all)	7	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	51 / 78 (65.38%)	53 / 83 (63.86%)	39 / 80 (48.75%)
occurrences (all)	233	187	159
Nausea			
subjects affected / exposed	29 / 78 (37.18%)	29 / 83 (34.94%)	13 / 80 (16.25%)
occurrences (all)	59	54	17
Constipation			
subjects affected / exposed	21 / 78 (26.92%)	16 / 83 (19.28%)	18 / 80 (22.50%)
occurrences (all)	29	19	20
Vomiting			
subjects affected / exposed	16 / 78 (20.51%)	21 / 83 (25.30%)	6 / 80 (7.50%)
occurrences (all)	30	35	9
Abdominal pain upper			
subjects affected / exposed	12 / 78 (15.38%)	9 / 83 (10.84%)	1 / 80 (1.25%)
occurrences (all)	15	16	1
Dyspepsia			
subjects affected / exposed	9 / 78 (11.54%)	3 / 83 (3.61%)	4 / 80 (5.00%)
occurrences (all)	11	3	4
Abdominal pain			
subjects affected / exposed	5 / 78 (6.41%)	11 / 83 (13.25%)	7 / 80 (8.75%)
occurrences (all)	5	13	11
Flatulence			
subjects affected / exposed	4 / 78 (5.13%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences (all)	4	2	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 78 (6.41%)	2 / 83 (2.41%)	1 / 80 (1.25%)
occurrences (all)	5	2	1
Rash			
subjects affected / exposed	2 / 78 (2.56%)	6 / 83 (7.23%)	3 / 80 (3.75%)
occurrences (all)	6	6	3
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 78 (0.00%)	0 / 83 (0.00%)	5 / 80 (6.25%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 78 (11.54%)	8 / 83 (9.64%)	10 / 80 (12.50%)
occurrences (all)	13	14	15
Pain in extremity			
subjects affected / exposed	9 / 78 (11.54%)	4 / 83 (4.82%)	7 / 80 (8.75%)
occurrences (all)	11	5	9
Bone pain			
subjects affected / exposed	5 / 78 (6.41%)	5 / 83 (6.02%)	0 / 80 (0.00%)
occurrences (all)	7	8	0
Muscular weakness			
subjects affected / exposed	5 / 78 (6.41%)	6 / 83 (7.23%)	4 / 80 (5.00%)
occurrences (all)	6	6	9
Arthralgia			
subjects affected / exposed	3 / 78 (3.85%)	11 / 83 (13.25%)	5 / 80 (6.25%)
occurrences (all)	4	13	6
Musculoskeletal pain			
subjects affected / exposed	3 / 78 (3.85%)	5 / 83 (6.02%)	1 / 80 (1.25%)
occurrences (all)	4	6	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 78 (2.56%)	6 / 83 (7.23%)	5 / 80 (6.25%)
occurrences (all)	2	6	5
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	20 / 78 (25.64%)	12 / 83 (14.46%)	21 / 80 (26.25%)
occurrences (all)	44	19	30
Respiratory tract infection			
subjects affected / exposed	13 / 78 (16.67%)	8 / 83 (9.64%)	8 / 80 (10.00%)
occurrences (all)	19	13	15
Urinary tract infection			
subjects affected / exposed	11 / 78 (14.10%)	8 / 83 (9.64%)	2 / 80 (2.50%)
occurrences (all)	13	10	2
Bronchitis			

subjects affected / exposed	9 / 78 (11.54%)	8 / 83 (9.64%)	1 / 80 (1.25%)
occurrences (all)	10	10	1
Conjunctivitis			
subjects affected / exposed	5 / 78 (6.41%)	4 / 83 (4.82%)	1 / 80 (1.25%)
occurrences (all)	5	5	1
Respiratory tract infection viral			
subjects affected / exposed	4 / 78 (5.13%)	0 / 83 (0.00%)	0 / 80 (0.00%)
occurrences (all)	6	0	0
Gastroenteritis			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	4 / 80 (5.00%)
occurrences (all)	2	1	5
Nasopharyngitis			
subjects affected / exposed	2 / 78 (2.56%)	6 / 83 (7.23%)	8 / 80 (10.00%)
occurrences (all)	2	10	13
Pneumonia			
subjects affected / exposed	2 / 78 (2.56%)	5 / 83 (6.02%)	4 / 80 (5.00%)
occurrences (all)	2	5	5
Influenza			
subjects affected / exposed	1 / 78 (1.28%)	4 / 83 (4.82%)	6 / 80 (7.50%)
occurrences (all)	1	4	7
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	14 / 78 (17.95%)	9 / 83 (10.84%)	7 / 80 (8.75%)
occurrences (all)	19	12	7
Decreased appetite			
subjects affected / exposed	13 / 78 (16.67%)	16 / 83 (19.28%)	10 / 80 (12.50%)
occurrences (all)	18	19	10
Hypocalcaemia			
subjects affected / exposed	7 / 78 (8.97%)	3 / 83 (3.61%)	4 / 80 (5.00%)
occurrences (all)	12	5	4
Hyponatraemia			
subjects affected / exposed	7 / 78 (8.97%)	1 / 83 (1.20%)	2 / 80 (2.50%)
occurrences (all)	12	2	4
Hypophosphataemia			
subjects affected / exposed	6 / 78 (7.69%)	6 / 83 (7.23%)	2 / 80 (2.50%)
occurrences (all)	10	15	4

Hyperglycaemia			
subjects affected / exposed	4 / 78 (5.13%)	7 / 83 (8.43%)	3 / 80 (3.75%)
occurrences (all)	5	12	8
Dehydration			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	4 / 80 (5.00%)
occurrences (all)	3	2	4
Muscle spasms			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	5 / 80 (6.25%)
occurrences (all)	1	2	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2017	• Participants with up to 4 prior lines of therapy were included with no limitation on how many participants could be treated with 3 or 4 prior lines of therapy. • Changed the platelet limit for inclusion to = 75 x 10^9/litre (L). Similar expectations applied for absolute neutrophil count (ANC); the ANC inclusion criterion was changed to = 1.0 x 10^9/L. • The bone marrow collection did not have to be repeated, unless participants received alternative anti-myeloma therapy between initial screening and re-screening. • Removal of the mandatory computed tomography/magnetic resonance imaging (CT/MRI) scan at screening if the clinical assessment of soft tissue plasmacytoma (STP) did not suggest the presence of a STP. This was in line with the post baseline assessments of STP when a CT/MRI was only mandatory in case STP was suspected by clinical assessment. • The anti-diarrhoeal medication entries and fluid intake entries were removed; participant's caregiver or a member of the participant's family were allowed to make the entries for the participant in case the participant was not able to make the entries her/himself. In addition, the electronic diary to document PAN/Dex dose administration was removed and allowed for this feature to be replaced by a paper diary as per local requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported