



Clinical trial results:

A Phase 3 Randomized, Controlled, Open-label Study of Selinexor, Bortezomib, and Dexamethasone (SVd) versus Bortezomib and Dexamethasone (Vd) in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

Summary

EudraCT number	2016-003957-14
Trial protocol	HU DE GR AT CZ BE ES BG PL IT
Global end of trial date	12 May 2022

Results information

Result version number	v1 (current)
This version publication date	28 May 2023
First version publication date	28 May 2023

Trial information

Trial identification

Sponsor protocol code	KCP-330-023
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03110562
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karyopharm Therapeutics Inc.
Sponsor organisation address	85 Wells Avenue, Newton, MA, United States, 02459
Public contact	Clinical Trials Information, Karyopharm Therapeutics Inc., +1 617658 0600, clinicaltrials@karyopharm.com
Scientific contact	Clinical Trials Information, Karyopharm Therapeutics Inc., +1 617658 0600, clinicaltrials@karyopharm.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	Interim
Date of interim/final analysis	12 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2020
Global end of trial reached?	Yes
Global end of trial date	12 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare progression-free survival (PFS) based on the Independent Review Committee (IRC's) disease outcome assessments in subjects randomised to the selinexor plus bortezomib plus low-dose dexamethasone (SVd) Arm versus the bortezomib plus low-dose dexamethasone (Vd) Arm.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki in place at the time of study conduct. The study was conducted in compliance with the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP] guideline CPMP/ICH/135/95), United States Code of Federal Code of Regulations, and all applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	India: 43

Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Serbia: 14
Country: Number of subjects enrolled	Ukraine: 45
Worldwide total number of subjects	402
EEA total number of subjects	183

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)	161
From 65 to 84 years	241
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 165 sites in 21 countries from 24-May-2017 to 12-May-2022.

Pre-assignment

Screening details:

A total of 402 Subjects were enrolled, of which 399 subjects received study treatment. Based on confirmed PD by the IRC, subjects who received Vd were allowed to cross over to receive either SVd (i.e., the SVdX treatment arm) or selinexor + low-dose dexamethasone (i.e., the SdX treatment arm) for those subjects who were intolerant to bortezomib.

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	SVd Arm: Selinexor + Bortezomib + Dexamethasone

Arm description:

Subjects received a fixed oral dose of 100 milligrams (mg) selinexor tablets (5 tablets of 20 mg each) once weekly (QW) on Days 1, 8, 15, 22, and 29 of each 35-day cycle, along with subcutaneous (SC) injection of 1.3 milligrams per square meter (mg/m²) bortezomib QW on Days 1, 8, 15, and 22 of each 35-day cycle, and an oral dose of 20 mg of dexamethasone twice weekly (BIW) on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.

Arm type	Experimental
Investigational medicinal product name	Selinexor
Investigational medicinal product code	KPT-330
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Selinexor was given as a fixed oral 100 mg dose (5 tablets of 20 mg each) on Days 1, 8, 15, 22, and 29 of each 35-day cycle (i.e., QW).

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Bortezomib was given at a dose of 1.3 mg/m² SC on Days 1, 8, 15, and 22 of each 35-day cycle (i.e., 4 out of every 5 weeks).

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

Dosage and administration details:

Dexamethasone was given as an oral 20 mg dose on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle (i.e., BIW).

Arm title	Vd Arm: Bortezomib + Dexamethasone
------------------	------------------------------------

Arm description:

Subjects received SC injection of 1.3 mg/m² bortezomib QW on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles, followed by greater than or equal to (\geq) 9 cycles on Days 1, 8, 15, and 22 of each 35-day cycle, and received oral dose of 20 mg dexamethasone BIW on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and for cycles \geq 9 on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Bortezomib was given at a dose of 1.3 mg/m² SC on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles, followed by \geq 9 cycles on Days 1, 8, 15, and 22 of each 35-day cycle.

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

Dosage and administration details:

Dexamethasone was given as an oral 20 mg dose BIW on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and for cycles \geq 9 on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

Number of subjects in period 1	SVd Arm: Selinexor + Bortezomib + Dexamethasone	Vd Arm: Bortezomib + Dexamethasone
Started	195	207
Completed	0	0
Not completed	195	207
Consent withdrawn by subject	37	35
Death	47	61
Ongoing	102	101
Unspecified	2	1
Lost to follow-up	7	6
Randomised but never treated	-	3

Baseline characteristics

Reporting groups

Reporting group title	SVd Arm: Selinexor + Bortezomib + Dexamethasone
-----------------------	---

Reporting group description:

Subjects received a fixed oral dose of 100 milligrams (mg) selinexor tablets (5 tablets of 20 mg each) once weekly (QW) on Days 1, 8, 15, 22, and 29 of each 35-day cycle, along with subcutaneous (SC) injection of 1.3 milligrams per square meter (mg/m²) bortezomib QW on Days 1, 8, 15, and 22 of each 35-day cycle, and an oral dose of 20 mg of dexamethasone twice weekly (BIW) on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.

Reporting group title	Vd Arm: Bortezomib + Dexamethasone
-----------------------	------------------------------------

Reporting group description:

Subjects received SC injection of 1.3 mg/m² bortezomib QW on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles, followed by greater than or equal to (\geq) 9 cycles on Days 1, 8, 15, and 22 of each 35-day cycle, and received oral dose of 20 mg dexamethasone BIW on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and for cycles \geq 9 on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.

Reporting group values	SVd Arm: Selinexor + Bortezomib + Dexamethasone	Vd Arm: Bortezomib + Dexamethasone	Total
Number of subjects	195	207	402
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	65.3	66.7	
standard deviation	\pm 9.56	\pm 9.35	-
Gender categorical			
Units: Subjects			
Female	80	92	172
Male	115	115	230
Race			
Units: Subjects			
Asian	25	25	50
Black or African American	4	7	11
White	161	165	326
Other	0	1	1
Missing	5	9	14
Ethnicity			
Units: Subjects			
Hispanic or Latino	6	5	11
Not Hispanic or Latino	171	188	359
Not Reported	14	11	25
Unknown	4	2	6
Missing	0	1	1

End points

End points reporting groups

Reporting group title	SVd Arm: Selinexor + Bortezomib + Dexamethasone
Reporting group description:	
Subjects received a fixed oral dose of 100 milligrams (mg) selinexor tablets (5 tablets of 20 mg each) once weekly (QW) on Days 1, 8, 15, 22, and 29 of each 35-day cycle, along with subcutaneous (SC) injection of 1.3 milligrams per square meter (mg/m ²) bortezomib QW on Days 1, 8, 15, and 22 of each 35-day cycle, and an oral dose of 20 mg of dexamethasone twice weekly (BIW) on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.	
Reporting group title	Vd Arm: Bortezomib + Dexamethasone
Reporting group description:	
Subjects received SC injection of 1.3 mg/m ² bortezomib QW on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles, followed by greater than or equal to (\geq) 9 cycles on Days 1, 8, 15, and 22 of each 35-day cycle, and received oral dose of 20 mg dexamethasone BIW on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and for cycles \geq 9 on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death, or sponsor decision to terminate the study.	

Primary: Progression-free Survival (PFS) as Assessed by IRC

End point title	Progression-free Survival (PFS) as Assessed by IRC
End point description:	
PFS: time from date of randomization until the first date of IRC-confirmed PD, per IMWG response criteria, or death due to any cause, whichever occurs first. PD: increase of 25% from lowest confirmed response value in 1 or more of the following criteria: a) serum M-protein with absolute increase of ≥ 0.5 g/dL; b) serum M-protein increase ≥ 1 g/dL if the lowest M-component was ≥ 5 g/dL; c) urine M-protein (absolute increase must be ≥ 200 mg per 24 hours); d) in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); e) in subjects without measurable serum and urine M-protein levels and without measurable involved FLC levels: bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be $\geq 10\%$). Intent-to-Treat population. "Number of subjects analysed"= subjects who were evaluable for this endpoint. "99999"= Upper limit of 95% CI was not estimated.	
End point type	Primary
End point timeframe:	
From date of randomization until IRC-confirmed documented PD or death, censored date, whichever occurred first (up to 32 months)	

End point values	SVd Arm: Selinexor + Bortezomib + Dexamethason e	Vd Arm: Bortezomib + Dexamethason e		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	124		
Units: Months				
median (confidence interval 95%)	13.93 (11.73 to 99999)	9.46 (8.11 to 10.78)		

Statistical analyses

Statistical analysis title	PFS as Assessed by IRC
Comparison groups	SVd Arm: Selinexor + Bortezomib + Dexamethasone v Vd Arm: Bortezomib + Dexamethasone
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0075
Method	Stratified Log-rank Test
Parameter estimate	Hazard Ratio (HR)
Point estimate	0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5279
upper limit	0.9335

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of randomization up to 30 days after last dose of treatment (up to 32 months)

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

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

Dictionary version	22.0
--------------------	------

Reporting groups

Reporting group title	SVd Arm: Selinexor + Bortezomib + Dexamethasone
-----------------------	---

Reporting group description:

Subjects received a fixed oral dose of 100 mg selinexor tablets (5 tablets of 20 mg each) QW on Days 1, 8, 15, 22, and 29 of each 35-day cycle, along with SC injection of 1.3 mg/m² bortezomib QW on Days 1, 8, 15, and 22 of each 35-day cycle, and an oral dose of 20 mg of dexamethasone BIW on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death or sponsor decision to terminate the study.

Reporting group title	Vd Arm: Bortezomib + Dexamethasone
-----------------------	------------------------------------

Reporting group description:

Subjects received SC injection of 1.3 mg/m² bortezomib QW on Days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles, followed by ≥ 9 cycles on Days 1, 8, 15, and 22 of each 35-day cycle, and received oral dose of 20 mg dexamethasone BIW on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and for cycles ≥ 9 on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle until PD confirmed by the IRC, investigator or subject decision to discontinue study treatment, pregnancy, unacceptable AEs or toxicity that could not be managed by supportive care, withdrawal of consent, death or sponsor decision to terminate the study.

Serious adverse events	SVd Arm: Selinexor + Bortezomib + Dexamethasone	Vd Arm: Bortezomib + Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 195 (51.79%)	77 / 204 (37.75%)	
number of deaths (all causes)	47	61	
number of deaths resulting from adverse events	12	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Ovarian neoplasm			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	

Pancreatic carcinoma metastatic subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Vascular disorders			
Blood pressure fluctuation subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Circulatory collapse subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Deep vein thrombosis subjects affected / exposed	1 / 195 (0.51%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Embolism subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hypotension subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Orthostatic hypotension subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Peripheral ischaemia subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Shock haemorrhagic			

subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 195 (1.03%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Chest pain			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Death			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
Fatigue			
subjects affected / exposed	2 / 195 (1.03%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
General physical health deterioration			
subjects affected / exposed	3 / 195 (1.54%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
Non-cardiac chest pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pyrexia			

subjects affected / exposed	3 / 195 (1.54%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Reproductive system and breast disorders			
Pelvic prolapse			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Bronchiectasis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Bronchospasm			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 195 (0.51%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Dyspnoea			
subjects affected / exposed	2 / 195 (1.03%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Epistaxis			

subjects affected / exposed	3 / 195 (1.54%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pulmonary embolism			
subjects affected / exposed	2 / 195 (1.03%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 11	0 / 12	
Pulmonary oedema			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 12	1 / 11	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Mixed anxiety and depressive disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Personality change			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Reactive psychosis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Investigations			

Blood glucose abnormal subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Injury, poisoning and procedural complications			
Cervical vertebral fracture subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Fall subjects affected / exposed	2 / 195 (1.03%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Femoral neck fracture subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Femur fracture subjects affected / exposed	2 / 195 (1.03%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hip fracture subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Injury subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
Overdose subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	

Pelvic fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Postoperative respiratory failure			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Rib fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Subdural haemorrhage			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Angina pectoris			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Atrial fibrillation			
subjects affected / exposed	4 / 195 (2.05%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Atrioventricular block			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Bradycardia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cardiac arrest			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Left ventricular dysfunction			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cardiac failure			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cardiac failure congestive			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
Cardiomyopathy			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Cardiovascular disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Left ventricular failure			

subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Myocardial infarction			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	1 / 12	0 / 11	
Myocardial ischaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	1 / 11	
Sinus tachycardia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Ventricular arrhythmia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Carotid artery aneurysm			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cerebral haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 12	0 / 11	
Cerebral infarction			

subjects affected / exposed	0 / 195 (0.00%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cerebral ischaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Encephalopathy			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hepatic encephalopathy			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Ischaemic stroke			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Metabolic encephalopathy			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Neuralgia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Neuropathy peripheral			

subjects affected / exposed	0 / 195 (0.00%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Paraesthesia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Presyncope			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Syncope			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Transient ischaemic attack			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Vascular dementia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 195 (2.56%)	3 / 204 (1.47%)	
occurrences causally related to treatment / all	2 / 5	2 / 3	
deaths causally related to treatment / all	1 / 11	0 / 12	
Febrile neutropenia			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Neutropenia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Thrombocytopenia			
subjects affected / exposed	3 / 195 (1.54%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Eye disorders			
Cataract			
subjects affected / exposed	4 / 195 (2.05%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 195 (0.00%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Colitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Colitis ischaemic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Constipation			
subjects affected / exposed	1 / 195 (0.51%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 12	0 / 11	
Diarrhoea			
subjects affected / exposed	7 / 195 (3.59%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	6 / 7	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Dyspepsia			

subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Nausea			
subjects affected / exposed	4 / 195 (2.05%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Vomiting			
subjects affected / exposed	7 / 195 (3.59%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Cholelithiasis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hepatic cirrhosis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Liver disorder			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	4 / 195 (2.05%)	2 / 204 (0.98%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	1 / 12	0 / 11	
Haematuria			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Bone pain			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Mobility decreased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Osteoarthritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Osteochondrosis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Spinal pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	

Infections and infestations Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 195 (1.54%) 1 / 3 1 / 12	2 / 204 (0.98%) 0 / 2 0 / 11	
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 195 (0.51%) 1 / 1 0 / 12	1 / 204 (0.49%) 0 / 1 0 / 11	
Chest wall abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 195 (0.00%) 0 / 0 0 / 12	1 / 204 (0.49%) 0 / 1 0 / 11	
Clostridium difficile colitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 195 (0.00%) 0 / 0 0 / 12	2 / 204 (0.98%) 0 / 2 0 / 11	
Clostridium difficile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 195 (0.51%) 0 / 1 0 / 12	0 / 204 (0.00%) 0 / 0 0 / 11	
Corona virus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 195 (0.51%) 1 / 1 0 / 12	0 / 204 (0.00%) 0 / 0 0 / 11	
Escherichia bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 195 (0.51%) 0 / 1 0 / 12	0 / 204 (0.00%) 0 / 0 0 / 11	
Gangrene subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 195 (0.00%) 0 / 0 0 / 12	1 / 204 (0.49%) 0 / 1 0 / 11	
Gastroenteritis			

subjects affected / exposed	4 / 195 (2.05%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
H1N1 influenza			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Infection			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Influenza			
subjects affected / exposed	3 / 195 (1.54%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Laryngitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Lower respiratory tract infection			
subjects affected / exposed	4 / 195 (2.05%)	3 / 204 (1.47%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 12	0 / 11	
Meningitis tuberculous			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia			

subjects affected / exposed	23 / 195 (11.79%)	24 / 204 (11.76%)	
occurrences causally related to treatment / all	6 / 23	8 / 24	
deaths causally related to treatment / all	3 / 12	3 / 11	
Orchitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia bacterial			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia fungal			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia influenzal			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 195 (1.03%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pulmonary sepsis			

subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 195 (1.03%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Sepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Septic shock			
subjects affected / exposed	4 / 195 (2.05%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	3 / 12	0 / 11	
Staphylococcal sepsis			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Upper respiratory tract infection			
subjects affected / exposed	3 / 195 (1.54%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Urinary tract infection			
subjects affected / exposed	4 / 195 (2.05%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Urosepsis			
subjects affected / exposed	3 / 195 (1.54%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Decreased appetite			
subjects affected / exposed	1 / 195 (0.51%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Dehydration			
subjects affected / exposed	3 / 195 (1.54%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hyperkalaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Hypokalaemia			
subjects affected / exposed	1 / 195 (0.51%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	
Tumour lysis syndrome			
subjects affected / exposed	0 / 195 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 12	0 / 11	

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

Non-serious adverse events	SVd Arm: Selinexor + Bortezomib + Dexamethasone	Vd Arm: Bortezomib + Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 195 (98.97%)	197 / 204 (96.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 195 (8.72%)	16 / 204 (7.84%)	
occurrences (all)	17	16	

Hypotension subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 10	11 / 204 (5.39%) 11	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	47 / 195 (24.10%) 47 82 / 195 (42.05%) 82 23 / 195 (11.79%) 23 28 / 195 (14.36%) 28	25 / 204 (12.25%) 25 37 / 204 (18.14%) 37 26 / 204 (12.75%) 26 21 / 204 (10.29%) 21	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	35 / 195 (17.95%) 35 18 / 195 (9.23%) 18 10 / 195 (5.13%) 10 10 / 195 (5.13%) 10 12 / 195 (6.15%) 12	30 / 204 (14.71%) 30 26 / 204 (12.75%) 26 8 / 204 (3.92%) 8 3 / 204 (1.47%) 3 4 / 204 (1.96%) 4	
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	16 / 195 (8.21%) 16	2 / 204 (0.98%) 2	

Insomnia subjects affected / exposed occurrences (all)	31 / 195 (15.90%) 31	32 / 204 (15.69%) 32	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 195 (6.67%) 13	7 / 204 (3.43%) 7	
Weight decreased subjects affected / exposed occurrences (all)	51 / 195 (26.15%) 51	25 / 204 (12.25%) 25	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 10	3 / 204 (1.47%) 3	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	13 / 195 (6.67%) 13	1 / 204 (0.49%) 1	
Headache subjects affected / exposed occurrences (all)	19 / 195 (9.74%) 19	11 / 204 (5.39%) 11	
Neuropathy peripheral subjects affected / exposed occurrences (all)	63 / 195 (32.31%) 63	96 / 204 (47.06%) 96	
Paraesthesia subjects affected / exposed occurrences (all)	5 / 195 (2.56%) 5	15 / 204 (7.35%) 15	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	71 / 195 (36.41%) 71	45 / 204 (22.06%) 45	
Leukopenia subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 10	3 / 204 (1.47%) 3	
Lymphopenia subjects affected / exposed occurrences (all)	11 / 195 (5.64%) 11	4 / 204 (1.96%) 4	

Neutropenia			
subjects affected / exposed	29 / 195 (14.87%)	12 / 204 (5.88%)	
occurrences (all)	29	12	
Thrombocytopenia			
subjects affected / exposed	116 / 195 (59.49%)	55 / 204 (26.96%)	
occurrences (all)	116	55	
Eye disorders			
Cataract			
subjects affected / exposed	39 / 195 (20.00%)	13 / 204 (6.37%)	
occurrences (all)	39	13	
Vision blurred			
subjects affected / exposed	13 / 195 (6.67%)	8 / 204 (3.92%)	
occurrences (all)	13	8	
Visual impairment			
subjects affected / exposed	11 / 195 (5.64%)	4 / 204 (1.96%)	
occurrences (all)	11	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 195 (7.69%)	11 / 204 (5.39%)	
occurrences (all)	15	11	
Constipation			
subjects affected / exposed	33 / 195 (16.92%)	34 / 204 (16.67%)	
occurrences (all)	33	34	
Diarrhoea			
subjects affected / exposed	60 / 195 (30.77%)	51 / 204 (25.00%)	
occurrences (all)	60	51	
Nausea			
subjects affected / exposed	98 / 195 (50.26%)	20 / 204 (9.80%)	
occurrences (all)	98	20	
Vomiting			
subjects affected / exposed	39 / 195 (20.00%)	9 / 204 (4.41%)	
occurrences (all)	39	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 195 (4.10%)	12 / 204 (5.88%)	
occurrences (all)	8	12	

Back pain subjects affected / exposed occurrences (all)	30 / 195 (15.38%) 30	28 / 204 (13.73%) 28	
Muscle spasms subjects affected / exposed occurrences (all)	3 / 195 (1.54%) 3	12 / 204 (5.88%) 12	
Pain in extremity subjects affected / exposed occurrences (all)	9 / 195 (4.62%) 9	17 / 204 (8.33%) 17	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	21 / 195 (10.77%) 21	18 / 204 (8.82%) 18	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	12 / 195 (6.15%) 12	8 / 204 (3.92%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	23 / 195 (11.79%) 23	10 / 204 (4.90%) 10	
Pneumonia subjects affected / exposed occurrences (all)	12 / 195 (6.15%) 12	9 / 204 (4.41%) 9	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	32 / 195 (16.41%) 32	29 / 204 (14.22%) 29	
Urinary tract infection subjects affected / exposed occurrences (all)	12 / 195 (6.15%) 12	9 / 204 (4.41%) 9	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	69 / 195 (35.38%) 69	11 / 204 (5.39%) 11	
Hypercreatininaemia subjects affected / exposed occurrences (all)	13 / 195 (6.67%) 13	7 / 204 (3.43%) 7	
Hyperglycaemia			

subjects affected / exposed	14 / 195 (7.18%)	11 / 204 (5.39%)	
occurrences (all)	14	11	
Hypocalcaemia			
subjects affected / exposed	15 / 195 (7.69%)	5 / 204 (2.45%)	
occurrences (all)	15	5	
Hypokalaemia			
subjects affected / exposed	18 / 195 (9.23%)	9 / 204 (4.41%)	
occurrences (all)	18	9	
Hyponatraemia			
subjects affected / exposed	15 / 195 (7.69%)	3 / 204 (1.47%)	
occurrences (all)	15	3	
Hypophosphataemia			
subjects affected / exposed	16 / 195 (8.21%)	6 / 204 (2.94%)	
occurrences (all)	16	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2017	<p>Amendment 1:</p> <ul style="list-style-type: none">• Added crossover to treatment with selinexor and dexamethasone (SdX) as an option for subjects in the Vd arm after PD was confirmed by the IRC if they had significant tolerability issues with bortezomib (e.g., higher than Grade 2 PN or Grade 2 or higher PN with pain).• Changed the third key secondary efficacy objective/endpoint from DOR to OS.• Revised the OS1 and time-to-next-treatment secondary objectives to add SdX and added a new exploratory objective (i.e., to assess disease response to SdX treatment) and endpoint (i.e., IMWG response criteria for subjects treated with SdX) for SdX to assess response for subjects who crossed over to SdX. Also clarified that for OS1, subjects on the Vd arm who crossed over were censored at the date of crossover.• Revised the definition of the time to response to "the duration of the time from randomization to the first documented response (\geq PR) per IMWG response criteria".• Updated the IMWG response criteria for myeloma to align with the most recent IMWG criteria (Kumar 2016). The definition for minimal residual disease was changed from "minor" to "minimal" response to align with the IMWG Consensus Criteria.• The process for crossover was modified to prevent premature crossover.• Revised exclusion 12 to clarify that subjects treated with an investigational anticancer therapy within 2 weeks before C1D1 were specifically excluded from the study.• Clarified that symptom-directed physical examinations were only to be performed if clinically indicated• Clarified that clinical plasmacytoma assessments are to be performed if clinically indicated at MM Disease Assessment Visits and at Durability of Response and Survival Follow-up Visits. Also corrected the window for detection of plasmacytomas at baseline by physical examination/palpation from "within 45 days" to "within 28 days" before C1D1.• Clarified that a skeletal survey was required at the End of Treatment Visit.

06 April 2017	<p>Amendment 2:</p> <ul style="list-style-type: none"> • Added details for the Interactive Response Technology system that was to be used to perform treatment randomization. • Added details for continuation of the study treatment for subjects if the study was terminated early to comply with International Council for Harmonisation Good Clinical Practice E6. • Clarified that double-barrier contraception methods were considered effective but not highly effective to align with the recommendations of the Clinical Trial Facilitation Group. Also clarified that sexual partners who were surgically sterilized were not exempt from the contraception requirements unless they were “permanently” surgically sterilized. • Added the requirement for pregnancy testing (serum human chorionic gonadotropin or urine) for females of childbearing potential before dosing on Day 1 of Cycles ≥ 2 to align with the recommendations of the Clinical Trial Facilitation Group. • For the PFS primary efficacy endpoint, changed the analysis to the stratified log-rank test and stratified Cox model (previously in Version 1.0 of the protocol). Also, specified that the stratified log-rank test was to be used for the secondary analyses of OS, DOR, and OS1, and that the exploratory analysis of the treatment discontinuation rate was to be performed using the stratified log-rank test. • For the ORR efficacy analysis, specified that subjects missing MM disease assessments after C1D1 were to be imputed as non-responders. • Changed the timing of the secondary analyses from “after significance is reached for PFS” to “at the time of ORR analysis” and specified that “statistical significance of the secondary endpoints will not be claimed until the ORR and PFS have reached significance.” • Changed the Hochberg procedure for testing the secondary endpoints to a hierarchical testing procedure.
17 August 2018	<p>Amendment 3:</p> <ul style="list-style-type: none"> • Changed ORR from a primary endpoint to a key secondary endpoint to address concerns expressed by the Agencies regarding including ORR as a primary endpoint (i.e., an analysis of ORR could jeopardize the integrity of the study for the ultimate assessment of PFS). • Revised the definition of “IRC-confirmed PD” and renamed the term as “IRC PD confirmation.” • Added a description of 8 tumor lysis syndrome cases reported across all of selinexor development as of May 2018. • Removed the split of the alpha level between PFS (0.02) and ORR (0.005) and added the assumed exponential dropout rate of 0.65%. • Revised the total number of PFS events required for the final analysis from 284 to 267, for the IA for sample size re-estimation from 85 to 81, and for the IA for futility or superiority from 213 to 201. • Removed the secondary OS1 objective/endpoint. • Removed the secondary objective/endpoint comparing ORR, PFS, and DOR for subjects with 1 versus >1 prior anti-MM regimen and added it as a subgroup exploratory analysis. • Revised the basis for the determination of the Revised International Staging System stage used in stratification of randomization from “at original MM diagnosis” to “at study entry, based on screening results.” • Added an exception to the requirement that subjects were to either remain on the study treatment until PD was confirmed by the IRC or until the subject discontinued the study treatment, completed the End of Treatment Visit, and was followed for survival. The exception only applied to subjects in the Vd arm who had to terminate bortezomib prior to IRC confirmed PD due to significant toxicities. • Revised inclusion criterion 12 for contraception requirements and guidance for pregnancy and breastfeeding. • Clarified the wording for how selinexor should be administered and removed the need to take selinexor with food.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported