Clinical trial results:
A phase 1b/2 trial to evaluate the safety of radium-223 dichloride (BAY 88-8223) in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

Summary

EudraCT number	2016-002438-58
Trial protocol	ES
Global end of trial date	20 March 2019

Results information

Result version number	v1 (current)
This version publication date	05 February 2020
First version publication date	05 February 2020

Trial information

Trial identification

Sponsor protocol code	18987

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02928029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	20 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b part (open-label)

1. To evaluate the safety of the combination of radium-223 dichloride plus bortezomib and dexamethasone

2. To determine the dose of radium-223 dichloride that will be used in the phase 2 part of the study (maximum tolerated dose [MTD] or recommended phase 2 dose [RP2D])

Phase 2 part (double-blind, randomized):

1. To evaluate the combined complete response (CR) + very good partial response (VGPR), as determined by International Myeloma Working Group (IMWG) uniform response criteria

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	7
EEA total number of subjects	1

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)	2
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 7 study centers, the first patient first visit was on 10/Feb/2017 and last patient last visit on 20/Mar/2019

Pre-assignment

Screening details:

10 subjects were enrolled in the study; 4 subjects in Cohort 1 and 6 subjects in Cohort 2. 3 of these subjects failed screening procedures, all for the reason "inclusion criteria not met". No subjects were started in the Phase 2 part of the study prior to study termination

Period 1

Period 1 title	Phase 1b (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone

Arm description:

Subjects received 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX

Arm type	Experimental
Investigational medicinal product name	Radium RA 223 dichloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

33 kBq/kg body weight, administered approximately 36 weeks: 6 doses; 1 dose every 6 weeks

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:

1.3 mg/m^2/dose, administered on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles.
For extended therapy beyond 8 cycles, BOR was administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment, or until progression-free survival (PFS) event occurred, the subject withdrew consent or an unacceptable toxicity developed, whichever occurred first.

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

Dosage and administration details:

40 mg, administered on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may have been split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator.
For extended therapy beyond 8 cycles, DEX was administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to 2 years after the first dose of study treatment or until a progression-free survival (PFS) event occurred, the subject withdrew consent or an unacceptable toxicity

developed, whichever occurs first

Arm title	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone

Arm description:

Subjects received 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX

Arm type	Experimental
Investigational medicinal product name	Radium RA 223 dichloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

55 kBq/kg body weight, administered approximately 36 weeks: 6 doses; 1 dose every 6 weeks

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:

1.3 mg/m^2/dose, administered on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles.
For extended therapy beyond 8 cycles, BOR was administered on Days 1 and 15 of a 28-day cycle for up to 2 years after the first dose of study treatment, or until progression-free survival (PFS) event occurred, the subject withdrew consent or an unacceptable toxicity developed, whichever occurred first.

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

Dosage and administration details:

40 mg, administered on Days 1, 4, 8, and 11 in a 21-day cycle, for 8 cycles. DEX administration may have been split over 2 days (on the day of BOR administration and the day after BOR administration) at the discretion of the Investigator.
For extended therapy beyond 8 cycles, DEX was administered orally at 20 mg/dose, on Days 1 and 15 of a 28-day cycle along with BOR for up to 2 years after the first dose of study treatment or until a progression-free survival (PFS) event occurred, the subject withdrew consent or an unacceptable toxicity developed, whichever occurs first

Number of subjects in period 1	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone
Started	3	4
Completed	0	0
Not completed	3	4
Clinical progression	1	2
Radiological progression	1	-

AE not related to clinical progression	1	1
Withdrawal by Subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone
Reporting group description:	
Subjects received 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX	
Reporting group title	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone
Reporting group description:	
Subjects received 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX	

Reporting group values	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone	Total
Number of subjects	3	4	7
Age Categorical Units: Subjects			
Adults (18-64 years)	1	1	2
Elderly (from 65-84 years)	2	3	5
Age Continuous Units: years			
arithmetic mean	65.0	68.3	
standard deviation	± 5.0	± 10.3	-
Gender Categorical Units: Subjects			
Female	1	2	3
Male	2	2	4
Race Units: Subjects			
White	0	2	2
Asian	2	2	4
Multiple	1	0	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	3	3	6
Hispanic or Latino	0	1	1

End points

End points reporting groups

Reporting group title	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone

Reporting group description:

Subjects received 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX

Reporting group title	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone

Reporting group description:

Subjects received 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223 dichloride doses in combination with BOR and DEX

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set consists of all subjects who received at least one administration of study treatment

Primary: Phase1: MTD/RP2D determined by the incidence of DLTs

End point title	Phase1: MTD/RP2D determined by the incidence of DLTs[1]

End point description:

Maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) determined by incidence of dose limiting toxicity (DLT) using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for the severity grade

End point type	Primary

End point timeframe:

From the start of study medication through 3 weeks after administration of the second dose of radium-223 dichloride

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: MTD/RP2D was not determined in this study

End point values	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: KBq/kg				
number (not applicable)				

Notes:

[2] - This study was stopped prior to the MTD being defined. Accordingly, there was no RP2D determined
[3] - This study was stopped prior to the MTD being defined. Accordingly, there was no RP2D determined

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: The number of subjects with treatment-emergent adverse events

(TEAEs), drug-related TEAEs, and treatment-emergent serious AE

End point title	Phase 1: The number of subjects with treatment-emergent adverse events (TEAEs), drug-related TEAEs, and treatment-emergent serious AE[4]

End point description:

A treatment-emergent adverse event (TEAE) is defined as any event arising or worsening after start of study drug administration until the end of the treatment period

End point type	Primary

End point timeframe:

From the start of study medication up to 30 days after the last dose of study medication

Notes:

[4] - 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: The statistical analysis for this end-point is descriptive

End point values	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: subjects				
Any TEAE	3	4		
Any drug-related TEAE	3	4		
Any treatment-emergent serious AE	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: The number of subjects with complete response (CR) and very good partial response (VGPR)

End point title	Phase 1: The number of subjects with complete response (CR) and very good partial response (VGPR)

End point description:

Determined by International Myeloma Working Group (IMWG) uniform response criteria.
CR: Negative immunofixation of serum and urine, disappearance of any soft-tissue plasmacytomas, and <5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum free light chain (FLC) level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; 2 consecutive assessments are needed.
VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-component plus urine M-component <100 mg/24 hours (hrs); in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; 2 consecutive assessments are needed

End point type	Secondary

End point timeframe:

Up to 2 years after last dose of study medication

End point values	Radium-223 dichloride 33 kBq/kg + Bortezomib and Dexamethasone	Radium-223 dichloride 55 kBq/kg + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: subjects				

Notes:

[5] - Subjects were not evaluable per International Myeloma Working Group (IMWG) uniform response criteria

[6] - Subjects were not evaluable per International Myeloma Working Group (IMWG) uniform response criteria

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of study medication up to 30 days after the last dose of study medication	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Radium-223 33 kBq/kg + BOR/DEX
Reporting group description:	
Subjects received 33 kiloBecquerel (kBq)/kg body weight every 6 weeks for a total of 6 radium-223dichloride doses in combination with BOR and DEX	
Reporting group title	Radium-223 55 kBq/kg + BOR/DEX
Reporting group description:	
Subjects received 55 kBq/kg body weight every 6 weeks for a total of 6 radium-223dichloride doses in combination with BOR and DEX	

Serious adverse events	Radium-223 33 kBq/kg + BOR/DEX	Radium-223 55 kBq/kg + BOR/DEX	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 4 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Radium-223 33 kBq/kg + BOR/DEX	Radium-223 55 kBq/kg + BOR/DEX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	
occurrences (all)	4	2	
Chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Face oedema			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Injection site reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Productive cough			

subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	
occurrences (all)	0	3	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	18	
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	16	
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	11	
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Periorbital oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vision blurred			

subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	
occurrences (all)	2	3	
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic dermatitis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Influenza			

subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Rhinovirus infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Septic arthritis streptobacillus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2017	• Due to changes in the therapies of choice for MM patients, daratumumab cohorts (Cohorts 3 and 4) were added to the study with significant changes to the study design introduced throughout the protocol to accommodate the new background treatment. • Radium-223 dichloride dose level of 88kBq/kg body weight was removed from the study. • The randomized phase 2 part of the study has been removed.
18 May 2018	• Due to feedback on the new study design presented in protocol amendment 1 received from some authorities and investigators, the daratumumab cohort was removed from the study. Consequently, the study protocol was revised to return to the original backbone treatment with only bortezomib/dexamethasone with a randomized expansion cohort in order to obtain more robust data on the anti-multiple myeloma activity of radium-223 dichloride in combination with bortezomib/dexamethasone. • Added the randomized phase 2 part of the study to all applicable sections, including phase 2 study objectives and randomization steps. • Clarifications were added related to MM and bone biomarker exploratory endpoints. • Added clarifications to the safety follow up for the collection of bone fracture and bone associated events and clarification added for the recommended use of bone health agents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As no subject entered phase 2, endpoints for this phase could not be listed due to system limitation

Notes: