Clinical trial results:
An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy(Including a Proteasome Inhibitor and Immunomodulatory drug (IMiD)) or are Double Refractory to a Proteasome Inhibitor and an IMiD

Summary

EudraCT number	2013-000752-18
Trial protocol	BE ES
Global end of trial date	30 May 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2018
First version publication date	02 June 2018

Trial information

Trial identification

Sponsor protocol code	CR102651

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01985126
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research and Development LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research and Development LLC, ClinicalTrialsEU@its.jnj.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	30 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to determine the efficacy of 2 daratumumab treatment regimens, as measured by the overall response rate (ORR) (partial response [PR] or better), in subjects with multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) or whose disease was double refractory to both a PI and an IMiD agent.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.The safety assessments included clinical laboratory tests (hematology and serum chemistry), vital sign measurements, electrocardiograms (ECGs), physical examinations and adverse events were reported throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	44 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United States: 90
Worldwide total number of subjects	124
EEA total number of subjects	12

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)	66
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 150 subjects were planned to enroll but 124 subjects were enrolled and analyzed in this study. Out of them, 59 subjects were enrolled in Part 1 and 65 subjects were enrolled in Part 2.

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	Daratumumab 8 mg/kg

Arm description:

Daratumumab 8 milligram per kilogram (mg/kg) every 4 weeks (Q4W) via intravenous (IV) route until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab 8 mg/kg Q4W as intravenous infusion.

Arm title	Daratumumab 16 mg/kg

Arm description:

Daratumumab 16 mg/kg weekly for 8 weeks; then every 2 weeks (Q2W) for 16 weeks; then Q4W via IV route until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab 16 mg/kg weekly for 8 weeks; then Q2W for 16 weeks; then Q4W until disease progression or unacceptable toxicity.

Number of subjects in period 1	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg
Started	18	106
Completed	0	0
Not completed	18	106
Consent withdrawn by subject	2	7
Other: study terminated by sponsor	1	22
Lost to follow-up	-	8
Other: death	15	69

Baseline characteristics

Reporting groups	
Reporting group title	Daratumumab 8 mg/kg
Reporting group description:	
Daratumumab 8 milligram per kilogram (mg/kg) every 4 weeks (Q4W) via intravenous (IV) route until disease progression or unacceptable toxicity.	
Reporting group title	Daratumumab 16 mg/kg
Reporting group description:	
Daratumumab 16 mg/kg weekly for 8 weeks; then every 2 weeks (Q2W) for 16 weeks; then Q4W via IV route until disease progression or unacceptable toxicity.	

Reporting group values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg	Total
Number of subjects	18	106	124
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	58	66
From 65 to 84 years	10	48	58
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	64.2	62.9	
standard deviation	± 7.72	± 10	-
Title for Gender Units: subjects			
Female	6	54	60
Male	12	52	64
Stage of Disease (ISS)			
The International Staging System (ISS) system consists of stage I: beta2-microglobulin less than (<)3.5 milligram/liter (mg/l) and albumin greater than or equal to (>=) 3.5 gram (g)/100 ml; stage II: neither stage I nor stage III and stage III: beta2-microglobulin >= 5.5 mg/l.			
Units: Subjects			
stage I	2	26	28
stage II	8	40	48
stage III	8	40	48
Number of Prior Lines of Therapy Units: Subjects			
<= 3 Lines	6	19	25
> 3 Lines	12	87	99
Refractory to Proteasome Inhibitor (PI)/ Immunomodulatory Drug (IMiD) Units: Subjects			
Both a PI and IMiD	15	101	116
PI only	1	3	4
IMiD only	0	1	1
None	2	1	3
Region of Enrollment Units: Subjects			

Canada	0	22	22
Spain	3	9	12
United States	15	75	90

End points

End points reporting groups

Reporting group title	Daratumumab 8 mg/kg
Reporting group description:	
Daratumumab 8 milligram per kilogram (mg/kg) every 4 weeks (Q4W) via intravenous (IV) route until disease progression or unacceptable toxicity.	
Reporting group title	Daratumumab 16 mg/kg
Reporting group description:	
Daratumumab 16 mg/kg weekly for 8 weeks; then every 2 weeks (Q2W) for 16 weeks; then Q4W via IV route until disease progression or unacceptable toxicity.	

Primary: Percentage of Subjects With Overall Response

End point title	Percentage of Subjects With Overall Response[1]
End point description:	
Overall response defined as percentage of subjects who achieved complete response (sCR), complete response (CR), very good partial response (VGPR) or (partial response)PR. Per IMWG criteria, sCR: defined as normal (free light chain) FLC ratio, and PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry; CR: Negative immunofixation on serum, urine and disappearance of tissue plasmacytomas and < 5% plasma cells in bone marrow; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or >= 90% reduction in serum M-protein plus urine M-protein level < 100mg/24 hrs; PR: >= 50% reduction of serum M-protein and reduction in 24 hrs urinary M-protein by >= 90% or to <200 mg/24 hrs; if serum and urine M-protein are not measurable, decrease of >=50% in difference between involved and uninvolved FLC levels is required in place of M-protein criteria. All treated analysis set included all subjects who received at least 1 dose of daratumumab.	
End point type	Primary
End point timeframe:	
Up to 14.4 Months	
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: Descriptive statistical analysis was performed for this endpoint.	

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	106		
Units: percentage of subjects				
number (confidence interval 95%)	11.1 (1.4 to 34.7)	29.2 (20.8 to 38.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
End point description:	
Duration of response was calculated from the date of initial documentation of a response (PR or better)	

to the date of first documented evidence of progressive disease, as defined in IMWG criteria. Disease progression (IMWG criteria): increase of 25 percent (%) from lowest response level in Serum M-component (the absolute increase must be >=0.5 g/dL) and/or; urine M-component (the absolute increase must be >=200 mg/24 hours) and/or; only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels (absolute increase must be >10 milligram per deciliter (mg/dL); Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 millimole per liter [mmol/L]) that can be attributed solely to the plasma cell proliferative disorder. Responders in all treated analysis set. Only those subjects with confirmed PR and those who experienced progressive disease (PD) were analyzed.

End point type	Secondary

End point timeframe:

Up to 14.4 Months

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[2]	31[3]		
Units: months				
median (confidence interval 95%)	99999 (1.8 to 99999)	7.4 (5.5 to 99999)		

Notes:

[2] - 99999: Median and UL of CI were inestimable due to less responders either progressed/died due to PD

[3] - 99999:Upper limit of CI was inestimable due to less responders either progressed or died due to PD

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) was defined as the number of days from administration of the first infusion (Day 1) to date of death. Median Overall Survival was estimated by using the Kaplan-Meier method. All treated analysis set included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Approximately up to 3 years

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	106		
Units: months				
median (confidence interval 95%)	19.45 (7.72 to 26.81)	18.60 (13.67 to 25.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Benefit

End point title	Percentage of Subjects With Clinical Benefit

End point description:

Clinical benefit rate defined as percentage of subjects who achieved minimal response (MR) or better. MR: >=25% but <= 49% reduction of serum M-protein and reduction in urine M-protein by 50%-89%. If present at baseline 25% to 49% reduction in size of soft tissue plasmacytomas. All treated analysis set included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 14.4 Months

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	106		
Units: percentage of subjects				
number (confidence interval 95%)	22.2 (6.4 to 47.6)	34.0 (25.0 to 43.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from the date of first dose of daratumumab to the date of initial documentation of a response (PR or better). Responders in all treated analysis set. Only those subjects with confirmed PR were analyzed.

End point type	Secondary

End point timeframe:

Up to 14.4 Months

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	31		
Units: months				
median (full range (min-max))	0.99 (0.95 to 1.02)	0.99 (0.9 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression free survival (PFS) was defined as the time between the date of first dose of daratumumab and either disease progression or death, whichever occurs first. PD as per IMWG criteria:increase of >=25% from lowest response level in Serum M-component and/or(absolute increase must be>=0.5gram/deciliter[g/dL])Urine M-component and/or(absolute increase must be>=200mg/24hr;only in subjects without measurable serum, urine M-protein levels:difference b/w involved, uninvolved FLC levels. Absolute increase must be >10mg/dL;Bone marrow plasma cell%:absolute% must be >=10%;Definite development of new bone lesions/soft tissue plasmacytomas/definite increase in size of existing bone lesions or soft tissue plasmacytomas;Development of hypercalcemia(corrected serum calcium>11.5mg/dL or 2.65millimol/liter[mmol/L])that can be attributed solely to plasma cell proliferative disorder. All treated analysis set included all subjects who received at least 1 dose of

End point type	Secondary

End point timeframe:

Up to 14.4 Months

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[4]	106		
Units: months				
median (confidence interval 95%)	4.86 (1.84 to 99999)	3.65 (2.76 to 4.63)		

Notes:

[4] - 99999: Upper limit of CI was not estimable due to the relatively short duration of follow-up.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression

End point description:

Time to progression was defined as the number of days from the date of first dose of daratumumab to the date of first record of disease progression. All treated analysis set included all subjects who received at least 1 dose of daratumumab.

End point type	Secondary

End point timeframe:

Up to 14.4 Months

End point values	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[5]	106		
Units: months				
median (confidence interval 95%)	4.86 (1.84 to 99999)	3.71 (2.79 to 5.39)		

Notes:

[5] - 99999: Median and upper limit for CI was not estimable' due to less number of subjects with events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Approximately up to 3.8 years	
Adverse event reporting additional description:	
All treated analysis set included all subjects who received at least 1 dose of daratumumab.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Daratumumab 8 mg/kg
Reporting group description:	
Daratumumab 8 milligram per kilogram (mg/kg) every 4 weeks (Q4W) via intravenous (IV) route until disease progression or unacceptable toxicity.	
Reporting group title	Daratumumab 16 mg/kg
Reporting group description:	
Daratumumab 16 mg/kg weekly for 8 weeks; then every 2 weeks (Q2W) for 16 weeks; then Q4W via IV until disease progression or unacceptable toxicity.	

Serious adverse events	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 18 (33.33%)	33 / 106 (31.13%)	
number of deaths (all causes)	15	69	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma Cell Leukaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 18 (5.56%)	5 / 106 (4.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (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			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			

subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen Saturation Abnormal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal Compression Fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal Incontinence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal Column Stenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 Influenza			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	4 / 106 (3.77%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Streptococcal			

subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 18 (0.00%)	4 / 106 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daratumumab 8 mg/kg	Daratumumab 16 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	105 / 106 (99.06%)	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	8 / 18 (44.44%)	12 / 106 (11.32%)	
occurrences (all)	9	18	
Hypotension			
subjects affected / exposed	2 / 18 (11.11%)	6 / 106 (5.66%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 18 (11.11%)	12 / 106 (11.32%)	
occurrences (all)	2	13	
Chest Discomfort			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Chills			
subjects affected / exposed	6 / 18 (33.33%)	10 / 106 (9.43%)	
occurrences (all)	7	10	
Fatigue			

subjects affected / exposed	6 / 18 (33.33%)	42 / 106 (39.62%)	
occurrences (all)	6	47	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 18 (5.56%)	6 / 106 (5.66%)	
occurrences (all)	2	6	
Oedema			
subjects affected / exposed	1 / 18 (5.56%)	2 / 106 (1.89%)	
occurrences (all)	1	3	
Oedema Peripheral			
subjects affected / exposed	2 / 18 (11.11%)	9 / 106 (8.49%)	
occurrences (all)	3	12	
Pain			
subjects affected / exposed	1 / 18 (5.56%)	6 / 106 (5.66%)	
occurrences (all)	1	6	
Pyrexia			
subjects affected / exposed	5 / 18 (27.78%)	20 / 106 (18.87%)	
occurrences (all)	5	22	
Immune system disorders			
Cytokine Release Syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Nipple Pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	2	
Prostatitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 18 (33.33%)	27 / 106 (25.47%)	
occurrences (all)	9	32	
Dyspnoea			
subjects affected / exposed	3 / 18 (16.67%)	18 / 106 (16.98%)	
occurrences (all)	5	18	
Dyspnoea Exertional			

subjects affected / exposed	1 / 18 (5.56%)	9 / 106 (8.49%)	
occurrences (all)	1	9	
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	9 / 106 (8.49%)	
occurrences (all)	0	10	
Nasal Congestion			
subjects affected / exposed	2 / 18 (11.11%)	22 / 106 (20.75%)	
occurrences (all)	2	26	
Oropharyngeal Pain			
subjects affected / exposed	1 / 18 (5.56%)	9 / 106 (8.49%)	
occurrences (all)	1	11	
Pleural Effusion			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Productive Cough			
subjects affected / exposed	1 / 18 (5.56%)	8 / 106 (7.55%)	
occurrences (all)	1	9	
Throat Irritation			
subjects affected / exposed	0 / 18 (0.00%)	7 / 106 (6.60%)	
occurrences (all)	0	7	
Wheezing			
subjects affected / exposed	1 / 18 (5.56%)	7 / 106 (6.60%)	
occurrences (all)	1	7	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	8 / 106 (7.55%)	
occurrences (all)	0	8	
Confusional State			
subjects affected / exposed	1 / 18 (5.56%)	7 / 106 (6.60%)	
occurrences (all)	1	8	
Depression			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Mental Status Changes			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	

Nervousness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 18 (5.56%)	4 / 106 (3.77%)	
occurrences (all)	1	4	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	3 / 18 (16.67%)	4 / 106 (3.77%)	
occurrences (all)	3	4	
Blood Creatinine Increased			
subjects affected / exposed	7 / 18 (38.89%)	9 / 106 (8.49%)	
occurrences (all)	7	21	
Blood Urea Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Transaminases Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Weight Decreased			
subjects affected / exposed	2 / 18 (11.11%)	5 / 106 (4.72%)	
occurrences (all)	2	6	
Weight Increased			
subjects affected / exposed	1 / 18 (5.56%)	4 / 106 (3.77%)	
occurrences (all)	1	5	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 18 (5.56%)	5 / 106 (4.72%)	
occurrences (all)	2	6	
Cardiac disorders			

Sinus Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Nervous system disorders			
Anaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	10 / 106 (9.43%)	
occurrences (all)	1	12	
Dysgeusia			
subjects affected / exposed	2 / 18 (11.11%)	3 / 106 (2.83%)	
occurrences (all)	2	3	
Encephalopathy			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 18 (11.11%)	13 / 106 (12.26%)	
occurrences (all)	2	17	
Hypoaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	6 / 106 (5.66%)	
occurrences (all)	1	7	
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 18 (5.56%)	6 / 106 (5.66%)	
occurrences (all)	1	7	
Sciatica			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	2 / 18 (11.11%)	2 / 106 (1.89%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	9 / 18 (50.00%)	39 / 106 (36.79%)	
occurrences (all)	20	101	
Leukopenia			
subjects affected / exposed	2 / 18 (11.11%)	8 / 106 (7.55%)	
occurrences (all)	2	18	
Lymphopenia			
subjects affected / exposed	3 / 18 (16.67%)	5 / 106 (4.72%)	
occurrences (all)	6	10	
Neutropenia			
subjects affected / exposed	2 / 18 (11.11%)	26 / 106 (24.53%)	
occurrences (all)	4	56	
Thrombocytopenia			
subjects affected / exposed	6 / 18 (33.33%)	28 / 106 (26.42%)	
occurrences (all)	17	71	
Ear and labyrinth disorders			
Cerumen Impaction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Ear Discomfort			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	4	
Abdominal Distension			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Abdominal Pain			
subjects affected / exposed	1 / 18 (5.56%)	7 / 106 (6.60%)	
occurrences (all)	1	8	
Aphthous Stomatitis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	19 / 106 (17.92%)	
occurrences (all)	1	21	
Diarrhoea			
subjects affected / exposed	4 / 18 (22.22%)	22 / 106 (20.75%)	
occurrences (all)	5	31	
Dry Mouth			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 18 (22.22%)	34 / 106 (32.08%)	
occurrences (all)	5	39	
Vomiting			
subjects affected / exposed	2 / 18 (11.11%)	19 / 106 (17.92%)	
occurrences (all)	2	22	
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Actinic Keratosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Nail Discolouration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Rash			

subjects affected / exposed	1 / 18 (5.56%)	2 / 106 (1.89%)	
occurrences (all)	1	2	
Rash Macular			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Bladder Spasm			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	2 / 18 (11.11%)	2 / 106 (1.89%)	
occurrences (all)	2	2	
Micturition Urgency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Urinary Incontinence			
subjects affected / exposed	2 / 18 (11.11%)	1 / 106 (0.94%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)	20 / 106 (18.87%)	
occurrences (all)	2	23	
Back Pain			
subjects affected / exposed	5 / 18 (27.78%)	25 / 106 (23.58%)	
occurrences (all)	5	27	
Bone Pain			
subjects affected / exposed	0 / 18 (0.00%)	10 / 106 (9.43%)	
occurrences (all)	0	12	
Flank Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Muscle Spasms			

subjects affected / exposed	2 / 18 (11.11%)	9 / 106 (8.49%)	
occurrences (all)	3	10	
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 18 (11.11%)	15 / 106 (14.15%)	
occurrences (all)	2	16	
Musculoskeletal Pain			
subjects affected / exposed	1 / 18 (5.56%)	12 / 106 (11.32%)	
occurrences (all)	1	14	
Myalgia			
subjects affected / exposed	0 / 18 (0.00%)	6 / 106 (5.66%)	
occurrences (all)	0	8	
Pain in Extremity			
subjects affected / exposed	1 / 18 (5.56%)	20 / 106 (18.87%)	
occurrences (all)	1	22	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	7 / 106 (6.60%)	
occurrences (all)	0	9	
Candida Infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	2 / 18 (11.11%)	4 / 106 (3.77%)	
occurrences (all)	2	4	
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	8 / 106 (7.55%)	
occurrences (all)	1	11	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	4 / 106 (3.77%)	
occurrences (all)	1	5	
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	7 / 106 (6.60%)	
occurrences (all)	1	11	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 18 (11.11%)	21 / 106 (19.81%)	
occurrences (all)	3	32	

Urinary Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	7 / 106 (6.60%)	
occurrences (all)	0	7	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	4 / 18 (22.22%)	19 / 106 (17.92%)	
occurrences (all)	4	21	
Fluid Retention			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	2 / 18 (11.11%)	16 / 106 (15.09%)	
occurrences (all)	4	28	
Hyperglycaemia			
subjects affected / exposed	3 / 18 (16.67%)	9 / 106 (8.49%)	
occurrences (all)	3	15	
Hyperkalaemia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	1	3	
Hyperuricaemia			
subjects affected / exposed	1 / 18 (5.56%)	4 / 106 (3.77%)	
occurrences (all)	1	4	
Hypoalbuminaemia			
subjects affected / exposed	4 / 18 (22.22%)	5 / 106 (4.72%)	
occurrences (all)	5	6	
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	3 / 106 (2.83%)	
occurrences (all)	2	9	
Hypoglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 106 (0.94%)	
occurrences (all)	1	3	
Hypokalaemia			
subjects affected / exposed	4 / 18 (22.22%)	11 / 106 (10.38%)	
occurrences (all)	4	17	
Hypomagnesaemia			

subjects affected / exposed	2 / 18 (11.11%)	8 / 106 (7.55%)	
occurrences (all)	2	19	
Hyponatraemia			
subjects affected / exposed	6 / 18 (33.33%)	7 / 106 (6.60%)	
occurrences (all)	7	7	
Hypophosphataemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	
Metabolic Acidosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 106 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	The overall reason for the amendment was to include the following changes: the sample size was increased to approximately 20 subjects per treatment group in Part 1 Stage 1 from an original 15 subjects, the study agent administration guidelines were changed from mg/hr to mL/hr, and minor additional changes were made for clarification throughout the protocol.
07 February 2014	The overall reason for the amendment was to include the following changes: following the discontinuation of the dose schedule of 8 mg/kg every 4 weeks (Treatment Group B) at the end of Stage 1, the number of subjects in Part 2 was increased to approximately 60 subjects, biomarker sampling time points were modified, and subjects in Group B were allowed to crossover to Group A.
09 July 2014	The overall reason for the amendment was to change the timing of the on treatment bone marrow biopsy.
08 June 2015	The overall reason for the amendment was to allow subjects who are benefiting from daratumamab to continue to receive study treatment beyond the previously defined end of study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported