



Clinical trial results:

A Prospective, Multicenter, Non-comparative, Open-label, Phase II Study to Evaluate the Effects of Daratumumab Monotherapy on Bone Parameters in Patients with Relapsed and/or Refractory Multiple Myeloma who Have Received at least 2 Prior Lines of Therapy including Lenalidomide and a Proteasome Inhibitor.

Summary

EudraCT number	2017-003951-44
Trial protocol	GR
Global end of trial date	26 March 2021

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	EAE-2017/MM01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03475628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Society of Hematology
Sponsor organisation address	27 Kifisias Ave, Athens, Greece, 11523
Public contact	info@heads-research.com, Health Data Specialists Ireland Limited, 0035 3906480600,
Scientific contact	info@heads-research.com, Health Data Specialists Ireland Limited, 0035 3906480600,

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	17 December 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate changes in bone resorption markers after 4 months of daratumumab monotherapy. Namely, C-telopeptide of collagen type 1 (CTX) and tartrate-resistant acid phosphatase-5b (TRACP-5b) will be evaluated.

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	12
From 65 to 84 years	44

Subject disposition

Recruitment

Recruitment details:

57 patients were enrolled and initiated study treatment across 6 sites in Greece. Among them, 33 had available results for bone resorption markers at baseline and at 4 months post-treatment onset. All 24 patients with no bone resorption markers at 4 months post-treatment onset discontinued treatment prior 4 months.

Pre-assignment

Screening details:

Patients who did not meet all the inclusion criteria or met any of the exclusion criteria were considered screening failures. Two patients signed an informed consent form and were screened but not enrolled (1 patient due to being lost-to follow-up during screening and 1 patient due to not fulfilling inclusion criteria).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Daratumuamb
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total dose: 16 mg/kg milligrams(s) / kilogram

Treatment with study design continues until disease progression, unacceptable toxicity (adverse event related to study drug), or the subject meets other criteria for discontinuation of study drug, for a maximum duration of 24 months.

Number of subjects in period 1	Daratumuamb
Started	57
Completed	18
Not completed	39
Consent withdrawn by subject	1
Death	38

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)
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Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	44	44	
85 years and over	1	1	
Age continuous Units: years			
median	73.0		
inter-quartile range (Q1-Q3)	65.0 to 79.0	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	26	26	
Ethnic Group Units: Subjects			
Greek	55	55	
Albanian	1	1	
Bulgarian	1	1	

End points

End points reporting groups

Reporting group title	Daratumuamb
Reporting group description:	-
Subject analysis set title	Intra-group
Subject analysis set type	Per protocol
Subject analysis set description:	
Baseline control group	

Primary: % Median Changes in Bone Resorption Marker, Namely C-telopeptide of Collagen Type 1 (CTX) From Baseline to 4 Months.

End point title	% Median Changes in Bone Resorption Marker, Namely C-telopeptide of Collagen Type 1 (CTX) From Baseline to 4 Months.
End point description:	Percent changes in bone resorption marker, namely C-telopeptide of collagen type 1 (CTX) from baseline to 4 months.
End point type	Primary
End point timeframe:	Assessed on baseline and after 4 months from initiation of daratumumab monotherapy.

End point values	Daratumuamb	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	33	33 ^[1]		
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
% change in CTX from baseline to 4 months	3.9 (-38.6 to 30.1)	0 (0 to 0)		

Notes:

[1] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Non-Parametric Statistical Hypothesis Test
Comparison groups	Daratumuamb v Intra-group
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.747
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - The primary efficacy variable, the median percent change in CTX from baseline to endpoint after 4 months of daratumumab monotherapy, was analyzed by means of an analysis of covariance (Wilcoxon) model with site as fixed effect and baseline value as covariate.

Primary: % Median Changes in Bone Resorption Marker, Namely Tartrate-resistant Acid Phosphatase-5b (TRACP-5b) From Baseline to 4 Months.

End point title	% Median Changes in Bone Resorption Marker, Namely
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Tartrate-resistant Acid Phosphatase-5b (TRACP-5b) From Baseline to 4 Months.

End point description:

Percent median changes in Bone Resorption Marker, namely tartrate-resistant acid phosphatase-5b (TRACP-5b) from Baseline to 4 months.

End point type Primary

End point timeframe:

Assessed on baseline and after 4 months from initiation of daratumumab monotherapy.

End point values	Daratumuamb	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	33	33		
Units: percent volume/volume				
median (inter-quartile range (Q1-Q3))				
% change in TRACP-5b from baseline to 4 months	-2.6 (-23.6 to 31.7)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Non-Parametric Statistical Hypothesis Test
Comparison groups	Daratumuamb v Intra-group
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.694
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - The primary efficacy variables, the percent median changes in TRACP-5B from baseline to endpoint after 4 months of daratumumab monotherapy, was analyzed by means of an analysis of covariance (Wilcoxon) model with site as fixed effect and baseline value as covariate.

Secondary: % Median Changes in Bone Formation Marker, bALP

End point title % Median Changes in Bone Formation Marker, bALP

End point description:

Percent median change from baseline in bone formation marker bALP (measured in U/L) after 4, 8 and 12 months of daratumumab monotherapy (or at the end of therapy).

4 months, N=33

8 months, N=18

12 months, N=14

End point type Secondary

End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change in bALP from baseline to 4 months	18.4 (-8.3 to 45.5)			
Percent change in bALP from baseline to 8 months	27.3 (-16.8 to 71.5)			
Percent change in bALP from baseline to 12 months	22.5 (-2.9 to 78.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Formation Marker, OC

End point title	% Median Changes in Bone Formation Marker, OC
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End point description:

Change from baseline in bone formation marker OC (measured in ng/ml) after 4, 8 and 12 months of daratumumab monotherapy (or at the end of therapy).

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

Median change from baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	92.6 (-18.1 to 352.1)			
Percent change from baseline to 8 months	267.2 (98.1 to 571.8)			
Percent change from baseline to 12 months	297.1 (29.2 to 447.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median changes in Bone Formation Marker, PINP

End point title	% Median changes in Bone Formation Marker, PINP
End point description:	
Median change from baseline in bone formation marker PINP (measured in ng/ml) after 4, 8 and 12 months of daratumumab monotherapy (or at the end of therapy).	
4 months, N=33	
8 months, N=18	
12 months, N=14	
End point type	Secondary
End point timeframe:	
From baseline up to 12 months of daratumumab monotherapy or at end of treatment.	

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	10.2 (-16.9 to 54.5)			
Percent change from baseline to 8 months	39.9 (6.9 to 264.9)			
Percent change from baseline to 12 months	34.0 (-19.5 to 162.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Resorption Marker, CTX

End point title	% Median Changes in Bone Resorption Marker, CTX
End point description:	
Median change from baseline in bone resorption marker CTX (measured in pg/ml) after 8 and 12 months of daratumumab monotherapy.	
8 months, N=18	
12 months, N=14	
End point type	Secondary
End point timeframe:	
From baseline up to 12 months of daratumumab monotherapy or at end of treatment.	

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 8 months	6.6 (-52.5 to 41.6)			

Percent change from baseline to 12 months	-33.9 (-79.4 to 0.9)			
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Statistical analyses

No statistical analyses for this end point

Secondary: % Median change in Bone Resorption Marker, TRACP-5b

End point title	% Median change in Bone Resorption Marker, TRACP-5b
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End point description:

Median change from baseline in bone resorption marker TRACP-5b (measured in mU/dL) after 8 and 12 months of daratumumab monotherapy.

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent volume/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 8 months	10.3 (-18.6 to 45.0)			
Percent change from baseline to 12 months	5.7 (-21.6 to 38.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Marker RANKL

End point title	% Median Changes in Bone Marker RANKL
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End point description:

Median change from baseline in RANKL (measured in pg/ml) after 4, 8 and 12 months of daratumumab monotherapy.

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	20.7 (-32.9 to 100.9)			
Percent change from baseline to 8 months	74.0 (-26.9 to 194.6)			
Percent change from baseline to 12 months	83.0 (23.4 to 121.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Marker Ratio,RANKL/OPG Ratio

End point title	% Median Changes in Bone Marker Ratio,RANKL/OPG Ratio
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End point description:

Median Change from baseline in RANKL/OPG ratio after 4, 8 and 12 months of daratumumab monotherapy.

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Ratio RANKL/OPG				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	3.80 (-39.29 to 147.06)			
Percent change from baseline to 8 months	48.30 (-38.62 to 270.33)			
Percent change from baseline to 12 months	57.11 (-15.91 to 179.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Marker CCL3

End point title	% Median Changes in Bone Marker CCL3
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End point description:

Median change from baseline in CCL3 (measured in pg/ml) after 4, 8 and 12 months of daratumumab monotherapy.

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	-16.0 (-34.4 to 6.0)			
Percent change from baseline to 8 months	-22.0 (-61.9 to 34.7)			
Percent change from baseline to 12 months	-26.1 (-63.3 to -1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Marker Dkk1

End point title	% Median Changes in Bone Marker Dkk1
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End point description:

Median change from baseline in Dkk1 (measured in ng/ml) after 4, 8 and 12 months of daratumumab monotherapy.

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	-17.5 (-42.5 to -4.9)			
Percent change from baseline to 8 months	-27.6 (-35.6 to -11.7)			
Percent change from baseline to 12 months	-38.3 (-54.1 to -30.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Changes in Bone Marker SOST

End point title	% Median Changes in Bone Marker SOST
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End point description:

Median change from baseline in SOST (measured in pmol/L) after 4, 8 and 12 months of daratumumab monotherapy.

4 months, N=33

8 months, N=18

12 months, N=14

End point type	Secondary
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End point timeframe:

From baseline up to 12 months of daratumumab monotherapy or at end of treatment.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent weight/volume				
median (inter-quartile range (Q1-Q3))				
Percent change from baseline to 4 months	2.7 (-32.2 to 69.3)			
Percent change from baseline to 8 months	-14.6 (-43.1 to 6.5)			
Percent change from baseline to 12 months	-16.5 (-48.8 to 187.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Changes in Bone Marker Activin-A

End point title	Median Changes in Bone Marker Activin-A
End point description: Change from baseline in activin-A (measured in µg/L) after 4, 8 and 12 months of daratumumab monotherapy. There are no available results due to insufficient sample tissue.	
End point type	Secondary
End point timeframe: From baseline up to 12 months of daratumumab monotherapy or at end of treatment.	

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[4]			
Units: percent weight/volume				
median (standard deviation)	()			

Notes:

[4] - There are no available results due to insufficient sample tissue.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunomodulatory Effects of Daratumumab on T Cells by Comprehensive Molecular and Phenotypic Studies and Correlations With Bone Markers.

End point title	Immunomodulatory Effects of Daratumumab on T Cells by Comprehensive Molecular and Phenotypic Studies and Correlations With Bone Markers.
End point description: The evaluation of the immunomodulatory effects of daratumumab on T cells by comprehensive molecular and phenotypic studies and correlations with bone markers. This was not a measurable outcome.	
End point type	Secondary
End point timeframe: Measured at baseline and after 3 and 6 months after initiation of daratumumab monotherapy.	

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[5]			
Units: Count				
number (not applicable)				

Notes:

[5] - This was not a measurable outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title | Progression Free Survival (PFS)

End point description:

Progression free survival is defined as the time, in months, from recruitment to the date of the first documented PD or death due to any cause, whichever comes first. PD was assessed by the investigator based on the analysis of serum and urine protein electrophoresis (sPEP and uPEP), serum free light chain protein (sFLC), Corrected serum calcium assessment, imaging and bone marrow assessments as per modified IMWG guidelines.

End point type | Secondary

End point timeframe:

From recruitment to the date of the first documented PD or death due to any cause, whichever comes first (approximately up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
median (confidence interval 95%)				
Median (95% Confidence Interval)	4.66 (2.98 to 7.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title | Overall Survival (OS)

End point description:

Overall survival is defined as the time, in months, from treatment start to the date of death from any cause.

End point type | Secondary

End point timeframe:

Time from first dose of study treatment to death (approximately up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
median (confidence interval 95%)				
Median (95% Confidence Interval)	10.46 (8.33 to 16.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment

End point title	Time to Next Treatment
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End point description:

Time to next therapy will be defined as the time, in months, from treatment start to the date of next anti-neoplastic therapy or death from any cause, whichever comes first.

End point type	Secondary
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End point timeframe:

From first dose until the date to next anti-neoplastic therapy or death from any cause, whichever comes first (approximately up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Months				
median (confidence interval 95%)				
Median (95% Confidence Interval)	7.10 (3.80 to 9.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of Pathological Fractures (Skeletal Surveys-Skeletal Related Events)

End point title	The Incidence of Pathological Fractures (Skeletal Surveys-Skeletal Related Events)
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End point description:

The incidence of pathological fractures will be evaluated in terms of number (and percentage) of patients with events and number of events per patient.

No skeletal-related events were observed during the study period.

End point type	Secondary
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End point timeframe:

From baseline to 24 months (up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[6]			
Units: Count				
number (not applicable)				

Notes:

[6] - No skeletal-related events were observed during the study period.

Statistical analyses

No statistical analyses for this end point

Secondary: Need for Radiotherapy or Surgery to the Bones (Skeletal Surveys-Skeletal Related Events)

End point title	Need for Radiotherapy or Surgery to the Bones (Skeletal Surveys-Skeletal Related Events)
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End point description:

Need for radiotherapy or surgery to the bones will be evaluated in terms of number (and percentage) of patients with events and number of events per patient.

No skeletal-related events were observed during the study period.

End point type	Secondary
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End point timeframe:

From baseline to 24 months (up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: Count				
number (not applicable)				

Notes:

[7] - No skeletal-related events were observed during the study period.

Statistical analyses

No statistical analyses for this end point

Secondary: Spinal Cord Compression (Skeletal Surveys-Skeletal Related Events)

End point title	Spinal Cord Compression (Skeletal Surveys-Skeletal Related Events)
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End point description:

Spinal cord compression will be evaluated in terms of number (and percentage) of patients with events and number of events per patient.

No skeletal-related events were observed during the study period.

End point type	Secondary
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End point timeframe:

From baseline to 24 months (up to 2 years).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[8]			
Units: Count				
number (not applicable)				

Notes:

[8] - No skeletal-related events were observed during the study period.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety (Adverse Events)

End point title	Safety (Adverse Events)
End point description:	The incidence of Adverse Events will be assessed according to the common Terminology Criteria for Adverse Events.
End point type	Secondary
End point timeframe:	Continuously throughout the study, starting from informed consent until 30 days after last study treatment (approximately up to 30 months).

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Count				
number (not applicable)				
Any (N)SAE	47			
Any NSAE	45			
Any SAE	19			
Any (N)SADR related to daratumumab	10			
Any NSADR related to daratumumab	7			
Any SADR related to daratumumab	4			
Any (N)SAE of Grade \geq 3	31			
Any (N)SAE of Grade 3 or 4	30			
Any fatal SAE	12			
At least one IRR	3			

Statistical analyses

No statistical analyses for this end point

Secondary: % Median Change in Bone Mineral Density (BMD) of lumbar spine

End point title	% Median Change in Bone Mineral Density (BMD) of lumbar spine
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End point description:

Median change in Bone Mineral Density (BMD) of lumbar spine measured by DXA after 6 and 12 months of daratumumab monotherapy.

End point type	Secondary
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End point timeframe:

Measured at baseline and after 6 and 12 months after initiation of daratumumab monotherapy.

End point values	Daratumuamb			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: score				
median (inter-quartile range (Q1-Q3))				
% change in T-score from baseline to 6 months	-3.2 (-192.3 to 10.5)			
% change in T-score from baseline to 12 months	3.2 (-47.4 to 28.0)			
% change in Z-score from baseline to 6 months	-186.4 (-200.0 to -15.4)			
% change in Z-score from baseline to 12 months	-81.8 (-333.3 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years.

Adverse event reporting additional description:

All patients who received at least one dose of study treatment were considered for data analysis. The incidence of adverse events (AEs) was tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 57 (33.33%)		
number of deaths (all causes)	38		
number of deaths resulting from adverse events	12		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac arrest			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Febrile neutropenia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	1 / 4		
Pneumonia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonia influenza			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 57 (78.95%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Vein rupture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	13 / 57 (22.81%)		
occurrences (all)	14		
Influenza like illness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		

Pyrexia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 3 4 / 57 (7.02%) 4		
Psychiatric disorders Dementia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1 1 / 57 (1.75%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased	1 / 57 (1.75%) 1 1 / 57 (1.75%) 1 5 / 57 (8.77%) 5 1 / 57 (1.75%) 1 3 / 57 (5.26%) 3		

subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5		
Neutrophil count decreased subjects affected / exposed occurrences (all)	8 / 57 (14.04%) 8		
Platelet count decreased subjects affected / exposed occurrences (all)	10 / 57 (17.54%) 14		
Serum ferritin decreased subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Injury, poisoning and procedural complications Spinal fracture subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Cardiac disorders Cardiac asthma subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Coronary artery disease subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Tachycardia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Nervous system disorders Confusional state subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Blood and lymphatic system disorders			

Anemia subjects affected / exposed occurrences (all)	25 / 57 (43.86%) 36		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2 3 / 57 (5.26%) 3 1 / 57 (1.75%) 1 2 / 57 (3.51%) 4		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Xeroderma subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1 1 / 57 (1.75%) 1		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) Back pain	2 / 57 (3.51%) 2		

subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Bone pain subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Muscular weakness subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Neck pain subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Infections and infestations			
Lower respiratory tract infection subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 9		
Otitis media subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 4		
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Iron deficiency			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2018	Amendment 1 The overall reason for the amendment was to clarify the timing of assessments.
02 July 2019	Amendment 2 The overall reason for the amendment was to include the new guidelines regarding HBV reactivation risk in patients receiving daratumumab treatment, and to clarify/update certain parts of the protocol.
08 June 2020	Amendment 3 The overall reason for the amendment was to update the protocol regarding the overall study duration from 30 to 36 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported