Clinical trial results:
A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab to Evaluate Daratumumab Retreatment

Summary

EudraCT number	2018-004185-34
Trial protocol	BE DE DK NL FR ES PL GR IT
Global end of trial date	10 January 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	54767414MMY2065

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03871829
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Antwerpseweg 15-17, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & 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	10 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of daratumumab subcutaneous (Dara-SC) in combination with carfilzomib and dexamethasone (Kd) with the efficacy of Kd in subjects with relapsed refractory multiple myeloma who were previously exposed to daratumumab to evaluate daratumumab retreatment.

Protection of trial subjects:

This 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 Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	88
EEA total number of subjects	58

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)	31
From 65 to 84 years	54
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 88 subjects were enrolled and treated, and none had completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Carfilzomib+Dexamethasone (Kd)

Arm description:

Subjects received carfilzomib 20 milligram per metre square (mg/m^2) intravenously (IV) on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and thereafter on Days 1, 8, 15 from Cycle 2 onwards. Subjects received dexamethasone 20 milligrams (mg) on Cycle 1 Days 1 and 2, and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2. Subjects received 40 mg on Days 1, 8, 15 and 22 for Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards.

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received carfilzomib 20 mg/m^2 on Cycle 1 Day 1 and 70 mg/m^2 on Cycle 1 Days 8 and 15, and thereafter on Days 1, 8, 15 from Cycle 2 onwards.

Arm title	Arm B: Dara-SC in combination with Kd (DKd)

Arm description:

Subjects received daratumumab 1800 mg by SC injection (Dara-SC) on Days 1, 8, 15, 22 of Cycles 1 and 2, Days 1 and 15 of Cycle 3-6, and on Day 1 from Cycle 7 onwards. Subjects received carfilzomib 20 mg/m^2 IV on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and Days 1, 8 and 15 from Cycle 2 onwards. Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Arm type	Experimental

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received daratumumab 1800 mg on Days 1, 8, 15, 22 for Cycle 1 and 2, Days 1 and 15 for Cycle 3-6, Day 1 from Cycle 7 onwards.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 for Cycle 1. Subjects received dexamethasone 40 mg IV or orally on days 1, 8, 15 and 22 for cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards.

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received carfilzomib 20 mg/m^2 on Cycle 1 Day 1 and 70 mg/m^2 on Cycle 1 Days 8 and 15 and Days 1, 8 and 15 from Cycle 2 onwards.

Number of subjects in period 1	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)
Started	44	44
Completed	0	0
Not completed	44	44
Adverse event, serious fatal	12	8
Consent withdrawn by subject	1	1
Study terminated by sponsor	31	34
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Carfilzomib+Dexamethasone (Kd)

Reporting group description:

Subjects received carfilzomib 20 milligram per metre square (mg/m^2) intravenously (IV) on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and thereafter on Days 1, 8, 15 from Cycle 2 onwards. Subjects received dexamethasone 20 milligrams (mg) on Cycle 1 Days 1 and 2, and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Reporting group title	Arm B: Dara-SC in combination with Kd (DKd)

Reporting group description:

Subjects received daratumumab 1800 mg by SC injection (Dara-SC) on Days 1, 8, 15, 22 of Cycles 1 and 2, Days 1 and 15 of Cycle 3-6, and on Day 1 from Cycle 7 onwards. Subjects received carfilzomib 20 mg/m^2 IV on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and Days 1, 8 and 15 from Cycle 2 onwards. Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Reporting group values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)	Total
Number of subjects	44	44	88
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	16	31
From 65 to 84 years	26	28	54
85 years and over	3	0	3
Title for AgeContinuous Units: years			
arithmetic mean	67.4	66.7	
standard deviation	± 8.56	± 9.72	-
Title for Gender Units: subjects			
Female	21	18	39
Male	23	26	49

End points

End points reporting groups

Reporting group title	Arm A: Carfilzomib+Dexamethasone (Kd)

Reporting group description:

Subjects received carfilzomib 20 milligram per metre square (mg/m^2) intravenously (IV) on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and thereafter on Days 1, 8, 15 from Cycle 2 onwards. Subjects received dexamethasone 20 milligrams (mg) on Cycle 1 Days 1 and 2, and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Reporting group title	Arm B: Dara-SC in combination with Kd (DKd)

Reporting group description:

Subjects received daratumumab 1800 mg by SC injection (Dara-SC) on Days 1, 8, 15, 22 of Cycles 1 and 2, Days 1 and 15 of Cycle 3-6, and on Day 1 from Cycle 7 onwards. Subjects received carfilzomib 20 mg/m^2 IV on Cycle 1 Day 1 and then 70 mg/m^2 on Cycle 1 Days 8 and 15, and Days 1, 8 and 15 from Cycle 2 onwards. Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 of Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 of Cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Each cycles were of 28 days.

Primary: Percentage of Subjects Achieving Very Good Partial Response (VGPR) or Better Response

End point title	Percentage of Subjects Achieving Very Good Partial Response (VGPR) or Better Response[1]

End point description:

VGPR or better rate was defined as the percentage of subjects achieving VGPR, complete response (CR), or stringent complete response (sCR) in accordance with the International Myeloma Working Group (IMWG) criteria, during/after the study treatment but before the start of subsequent anti-myeloma therapy. IMWG criteria: VGPR: Serum and urine M-component detected by immunofixation but not on electrophoresis, or greater than or equal to (>=)90 percent (%) reduction in serum Mprotein plus urine M-protein less than (<)100 milligram (mg)/24hours; CR: Negative immunofixation on the serum and urine, and Disappearance of any soft tissue plasmacytomas (PCs), and <5% PCs in bone marrow; sCR: CR plus normal free light chain (FLC) ratio, and Absence of clonal PCs by immunohistochemistry, immunofluorescence or 2 to 4 color flow cytometry. The response-evaluable analysis set included subjects who had confirmed diagnosis of multiple myeloma (MM) and measurable disease at baseline or screening visit.

End point type	Primary

End point timeframe:

Up to 3 years and 7 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 statistics was done, no inferential statistical analysis was performed.

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: Percentage of subjects				
number (confidence interval 90%)	46.2 (32.3 to 60.4)	48.8 (35.1 to 62.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the proportion of subjects who achieved partial response [PR] or better responses based on the computerized algorithm, in accordance with the IMWG criteria. IMWG criteria for PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or <200 mg/24 hours; If the serum and urine M-protein were not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels was required in place of the M-protein criteria; If serum and urine M-protein were not measurable, and serum free light assay is also not measurable, >=50% reduction in bone marrow plasma cells (PCs) was required in place of M-protein, provided baseline bone marrow plasma cell percentage was >=30%; additionally, if present at baseline, >=50% reduction in the size of soft tissue PCs was also required. The response-evaluable analysis set included subjects who had confirmed diagnosis of MM and measurable disease at baseline or screening visit.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: Percentage of subjects				
number (confidence interval 90%)	64.1 (49.7 to 76.8)	75.6 (62.1 to 86.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the duration from the date of randomisation to either progressive disease (PD) or death, whichever comes first. IMWG criteria: PD: >=25% from lowest response level in serum M-component and/or in urine M-component; only in subjects without measurable serum and urine M-protein levels: increase of >=25% in the difference between involved and uninvolved FLC levels and the absolute increase must be >10 mg/dL. BMPC%: the absolute % must be >=10%; definite increase in size of existing bone lesions or soft tissue plasmacytomas; definite development of new bone lesions or soft tissue plasmacytomas; development of hypercalcemia (corrected serum calcium >11.5 milligrams

per deciliter (mg/dL) or 2.65 millimoles per liter [mmol/L]) that can be attributed solely to PC proliferative disorder. Intent-to-treat (ITT) analysis set included all subjects who were randomised in the study. Here, 'N' (number of subjects analysed) signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	24		
Units: months				
median (confidence interval 90%)	10.61 (4.70 to 19.88)	10.74 (7.49 to 16.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Complete Response (CR) or Better

End point title	Percentage of Subjects Achieving Complete Response (CR) or Better

End point description:

Percentage of subjects achieving CR or better were reported. CR or better rate was defined as the proportion of subjects achieving CR or sCR based on the computerized algorithm, according to IMWG response criteria. IMWG criteria for CR: Negative immunofixation on the serum and urine, and Disappearance of any soft tissue plasmacytomas (PCs), and <5% PCs in bone marrow. The response-evaluable analysis set included subjects who had confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: Percentage of subjects				
number (confidence interval 90%)	25.6 (14.6 to 39.6)	12.2 (4.9 to 23.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomisation to the date of the subject's death due to any cause. ITT analysis set analysis set included all subjects who were randomised in the study. Here, 'N' (number of subjects analysed) signifies subjects who were evaluable for this outcome measure. Here, 99999 signifies data was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: months				
median (confidence interval 90%)	99999 (25.40 to 99999)	99999 (27.10 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Daratumumab

End point title	Serum Concentrations of Daratumumab[2]

End point description:

Serum concentrations of daratumumab were assessed. Pharmacokinetic (PK) analysis set included all subjects who had received at least 1 dose of daratumumab subcutaneous (dara-SC) and had at least 1 post-dose PK sample. Here, 'N' (number of subjects analysed) signifies subjects who were evaluable for this endpoint and 'n' (number analysed) signifies number of subjects analysed at each specified timepoints. This outcome measure was planned to be analysed for specified arm only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 3 Day 1, Cycle 7 Day 1 (each cycle of 28 days) and Follow Up (post treatment Week 8)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome measure was planned to be analysed for specified arm only.

End point values	Arm B: Dara-SC in combination with Kd (DKd)			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: microgram per millilitres (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day1 (n=6)	39.1 (± 44.1)			
Cycle 3 Day 1 (n=22)	849 (± 329)			
Cycle 7 Day 1 (n=19)	715 (± 381)			
Post-treatment Week 8 (n=4)	85.5 (± 131)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Negative Minimal Residual Disease (MRD)

End point title	Percentage of Subjects With Negative Minimal Residual Disease (MRD)

End point description:

Percentage of subjects with negative MRD were reported. MRD negativity rate, defined as the proportion of subjects who had MRD negative status at 10^-5 by bone marrow aspirate after the date of randomisation and prior to PD or subsequent anti-myeloma therapy. MRD negativity rate, defined as the proportion of subjects who have MRD negative status at 10-5 by bone marrow aspirate after the date of randomization and prior to PD or subsequent anti-myeloma therapy. ITT analysis set analysis set included all subjects who were randomised in the study.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: Percentage of subjects				
number (confidence interval 95%)	11.4 (3.8 to 24.6)	6.8 (1.4 to 18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment

End point title	Time to Next Treatment

End point description:

Time to next treatment was defined as the time from randomisation to the start of the next-line treatment. ITT analysis set analysis set included all subjects who were randomised in the study. Here, 'N' (number of subjects analysed) signifies subjects who were evaluable for this endpoint. Here, 99999 signifies data was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 3 years and 7 months

End point values	Arm A: Carfilzomib+Dexamethasone (Kd)	Arm B: Dara-SC in combination with Kd (DKd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	15		
Units: months				
median (confidence interval 90%)	20.60 (14.06 to 25.40)	20.14 (11.33 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-recombinant Human Hyaluronidase (rHuPH20) Antibodies

End point title	Number of Subjects with Anti-recombinant Human Hyaluronidase (rHuPH20) Antibodies[3]

End point description:

Number of subjects with rHuPH20 antibodies were reported. The immunogenicity analysis set for dara-SC included all randomised subjects who had appropriate samples for detection of the antibodies. This outcome measure was planned to be analysed for specified arm only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 3 Day 1, Cycle 7 Day 1 (each cycle of 28 days) and Follow Up (post treatment Week 8)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure was planned to be analysed for specified arm only.

End point values	Arm B: Dara-SC in combination with Kd (DKd)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-Daratumumab Antibodies

End point title	Number of Subjects with Anti-Daratumumab Antibodies[4]

End point description:

Number of subjects who test positive for anti-daratumumab antibodies were reported. The immunogenicity analysis set for dara-SC included all randomised subjects who had appropriate samples for detection of the antibodies. This outcome measure was planned to be analysed for specified arm only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 3 Day 1, Cycle 7 Day 1 (each cycle of 28 days) and Follow Up (post treatment Week 8)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure was planned to be analysed for specified arm only.

End point values	Arm B: Dara-SC in combination with Kd (DKd)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 3 years and 7 months

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Arm B: Dara-SC in combination with Kd (DKd)

Reporting group description:

Subjects received daratumumab subcutaneous (Dara-SC) 1800 mg by SC injection on Days 1, 8, 15, 22 for Cycle 1 and 2, Days 1 and 15 for Cycle 3-6, Day 1 from Cycle 7 onwards. Subjects received carfilzomib 20 mg/m^2 IV on Cycle 1 Day 1 and then 70 mg/m^2 on Day 8 and 15 of Cycle 1 and Days 1, 8 and 15 of Cycle 2. Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 for Cycle 1. Subjects then received dexamethasone 40 mg on days 1, 8, 15 and 22 for cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first.

Reporting group title	Arm A: Carfilzomib+Dexamethasone (Kd)

Reporting group description:

Subjects received carfilzomib 20 milligram per square meter (mg/m^2) intravenously (IV) on Day 1 of Cycle 1 and then 70 mg/m^2 on Days 8 and 15 of Cycle 1 and thereafter on Days 1, 8, 15 from Cycle 2 onwards. Subjects received dexamethasone 20 mg on Cycle 1 Days 1 and 2 and 40 mg IV or orally on Days 8, 15, 22 for Cycle 1. Subjects then received dexamethasone 40 mg IV or orally on Days 1, 8, 15 and 22 for cycles 2-9, then on Days 1, 8, 15 from Cycle 10 onwards, until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first.

Serious adverse events	Arm B: Dara-SC in combination with Kd (DKd)	Arm A: Carfilzomib+Dexamethasone (Kd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 43 (27.91%)	20 / 43 (46.51%)	
number of deaths (all causes)	7	12	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
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	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombocytopenia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Noninfective sialoadenitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 43 (0.00%)	4 / 43 (9.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia sepsis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

COVID-19			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Bacteraemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)	4 / 43 (9.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B: Dara-SC in combination with Kd (DKd)	Arm A: Carfilzomib+Dexamethasone (Kd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 43 (86.05%)	39 / 43 (90.70%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 43 (25.58%)	7 / 43 (16.28%)	
occurrences (all)	34	13	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 43 (11.63%)	4 / 43 (9.30%)	
occurrences (all)	9	4	
Oedema peripheral			
subjects affected / exposed	5 / 43 (11.63%)	3 / 43 (6.98%)	
occurrences (all)	6	3	
Malaise			
subjects affected / exposed	0 / 43 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	4	
Fatigue			
subjects affected / exposed	7 / 43 (16.28%)	3 / 43 (6.98%)	
occurrences (all)	11	4	
Catheter site pain			
subjects affected / exposed	0 / 43 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Asthenia			
subjects affected / exposed	5 / 43 (11.63%)	6 / 43 (13.95%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 43 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	7 / 43 (16.28%)	4 / 43 (9.30%)	
occurrences (all)	13	6	
Cough			

subjects affected / exposed	6 / 43 (13.95%)	5 / 43 (11.63%)	
occurrences (all)	7	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Insomnia			
subjects affected / exposed	2 / 43 (4.65%)	6 / 43 (13.95%)	
occurrences (all)	2	11	
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 43 (9.30%)	2 / 43 (4.65%)	
occurrences (all)	7	2	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	2 / 43 (4.65%)	7 / 43 (16.28%)	
occurrences (all)	2	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 43 (25.58%)	14 / 43 (32.56%)	
occurrences (all)	20	37	
Leukopenia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 43 (2.33%)	
occurrences (all)	5	2	
Lymphopenia			
subjects affected / exposed	3 / 43 (6.98%)	8 / 43 (18.60%)	
occurrences (all)	15	14	
Neutropenia			
subjects affected / exposed	8 / 43 (18.60%)	4 / 43 (9.30%)	
occurrences (all)	18	6	
Thrombocytopenia			
subjects affected / exposed	16 / 43 (37.21%)	8 / 43 (18.60%)	
occurrences (all)	77	32	
Eye disorders			

Cataract			
subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 43 (11.63%)	5 / 43 (11.63%)	
occurrences (all)	9	5	
Nausea			
subjects affected / exposed	6 / 43 (13.95%)	7 / 43 (16.28%)	
occurrences (all)	14	7	
Diarrhoea			
subjects affected / exposed	4 / 43 (9.30%)	11 / 43 (25.58%)	
occurrences (all)	8	14	
Constipation			
subjects affected / exposed	1 / 43 (2.33%)	4 / 43 (9.30%)	
occurrences (all)	2	5	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Renal impairment			
subjects affected / exposed	1 / 43 (2.33%)	5 / 43 (11.63%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	5	1	
Back pain			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	
occurrences (all)	5	6	
Arthralgia			
subjects affected / exposed	2 / 43 (4.65%)	4 / 43 (9.30%)	
occurrences (all)	2	5	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 43 (4.65%)	9 / 43 (20.93%)	
occurrences (all)	3	12	
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	
occurrences (all)	2	4	
COVID-19			
subjects affected / exposed	9 / 43 (20.93%)	9 / 43 (20.93%)	
occurrences (all)	9	10	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 43 (6.98%)	4 / 43 (9.30%)	
occurrences (all)	4	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2019	The purpose of the amendment was to include the language clarifying the need for contraception for all subjects to continue for 3 months after the end of study treatment as well as the caution for women who are at high risk for thrombosis to use other means of birth control other than hormonal birth control which carries the highest risk of thrombosis.
13 June 2021	The purpose of this amendment was to expand eligibility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported