Clinical trial results:
A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma

Summary

EudraCT number	2016-003554-33
Trial protocol	GR AT BE HU BG PL CZ FR ES GB RO
Global end of trial date	15 April 2022

Results information

Result version number	v1 (current)
This version publication date	30 April 2023
First version publication date	30 April 2023

Trial information

Trial identification

Sponsor protocol code	20160275

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03158688
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.com
Scientific contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.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	15 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare carfilzomib, dexamethasone, and daratumumab (KdD) to carfilzomib and dexamethasone (Kd) in terms of progression free survival (PFS) in participants with multiple myeloma who have relapsed after 1 to 3 prior therapies.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	58 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 60
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Greece: 43
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Poland: 48
Country: Number of subjects enrolled	Romania: 32
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Turkey: 27
Country: Number of subjects enrolled	United Kingdom: 7

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	466
EEA total number of subjects	240

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)	240
From 65 to 84 years	226
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 102 centers. 569 participants were screened and 466 were enrolled. Primary analysis (PA) data cutoff (DCO): 14-Jul-2019. Final analysis (FA) DCO: 15-Apr-2022.

Pre-assignment

Screening details:

Participants were randomized in 1:2 ratio to arms KD vs KdD after being stratified by 1) International Staging System (ISS) stage (Stage 1-2 vs Stage 3) at screening, 2) prior proteasome inhibitor exposure (yes/no), 3) number of prior lines of therapy (1 vs ≥ 2), and 4) prior cluster differentiation antigen 38 (CD38) antibody therapy (yes/no).

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	Kd - Carfilzomib and Dexamethasone

Arm description:

Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16 and at 40 mg on day 22 of all 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	KYPROLIS®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib for infusion was supplied as a lyophilized, sterile product in single-use vials. The lyophilized product was reconstituted with preservative-free sterile water for injection, the reconstituted solution contained carfilzomib 2 mg/mL. IV injections lasted approximately 30 minutes.

Dose could be modified based on a >20% change in body weight or toxicity.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Commercially available oral and intravenous (IV) formulas were obtained by investigative sites. Amgen supplied IV or orally (PO) dexa for some countries (Poland, Hungry, Romania, Bulgaria, Korea). Dosage modification rules applied based on participant age (participants > 75 years were given lower doses), dexa-related toxicities, and discontinuation of carfilzomib.

Arm title	KdD - Carfilzomib, Dexamethasone and Daratumumab

Arm description:

Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16

and at 40 mg on day 22 of all 28-day cycles. The administration of dexamethasone was given on carfilzomib and/or daratumumab IV infusion days. Daratumumab was administered by IV at 8 mg/kg on Cycle 1: days 1 and 2; at 16 mg/kg on Cycle 1: days 8, 15 and 22, and Cycle 2: days 1, 8, 15, and 22. The 16 mg/kg dosage was continued on Cycles 3-6: days 1 and 15. The 16 mg/kg dosage was continued on Cycles 7+: day 1 only.

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

Dosage and administration details:

Commercially available oral and intravenous (IV) formulas were obtained by investigative sites. Amgen supplied IV or PO dexa for some countries (Poland, Hungry, Romania, Bulgaria, Korea). Dosage modification rules applied based on participant age (participants > 75 years were given lower doses), dexa-related toxicities, and discontinuation of carfilzomib.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	DARZALEX®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab was supplied as a concentrated solution for infusion in single-use vials.

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	KYPROLIS®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carfilzomib for infusion was supplied as a lyophilized, sterile product in single-use vials. The lyophilized product was reconstituted with preservative-free sterile water for injection, the reconstituted solution contained carfilzomib 2 mg/mL. IV injections lasted approximately 30 minutes.

Dose could be modified based on a >20% change in body weight or toxicity.

Number of subjects in period 1	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab
Started	154	312
Treated	153	308
Completed	49	102
Not completed	105	210
Adverse event, serious fatal	74	142
Consent withdrawn by subject	14	28
Lost to follow-up	4	3
Decision by sponsor	13	37

Baseline characteristics

Reporting groups	
Reporting group title	Kd - Carfilzomib and Dexamethasone
Reporting group description:	
Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16 and at 40 mg on day 22 of all 28-day cycles.	
Reporting group title	KdD - Carfilzomib, Dexamethasone and Daratumumab
Reporting group description:	
Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16 and at 40 mg on day 22 of all 28-day cycles. The administration of dexamethasone was given on carfilzomib and/or daratumumab IV infusion days. Daratumumab was administered by IV at 8 mg/kg on Cycle 1: days 1 and 2; at 16 mg/kg on Cycle 1: days 8, 15 and 22, and Cycle 2: days 1, 8, 15, and 22. The 16 mg/kg dosage was continued on Cycles 3-6: days 1 and 15. The 16 mg/kg dosage was continued on Cycles 7+: day 1 only.	

Reporting group values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab	Total
Number of subjects	154	312	466
Age Categorical			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: participants			
18 - 64 years	77	163	240
65 - 74 years	55	121	176
75 - 84 years	22	28	50
>=85 years	0	0	0
Age Continuous			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: years			
arithmetic mean	64.3	62.9	
standard deviation	± 9.6	± 10.0	-
Sex: Female, Male			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: participants			
Female	63	135	198
Male	91	177	268
Ethnicity (NIH/OMB)			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
Hispanic or Latino	1	7	8
Not Hispanic or Latino	146	291	437
Unknown or Not Reported	7	14	21
Race/Ethnicity, Customized			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
Asian	20	46	66

Black or African American	2	7	9
White	123	243	366
Other	9	16	25
Frailty Status as Assessed by Investigator			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
Fit	68	176	244
Intermediate fitness	36	54	90
Frail	9	10	19
Not available	37	66	103
Missing	4	6	10
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead. Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
Disease status 0 or 1	147	295	442
Disease status 2	7	15	22
Missing	0	2	2
Risk Group as Determined by Fluorescent in situ Hybridization (FISH)			
The high-risk group consists of the genetic subtypes t(4; 14), t(14; 16), or deletion17p. The standard-risk group consists of participants without t(4; 14), t(14; 16), and deletion 17p. The unknown risk group is participants with FISH result not done, failed or quantity was not sufficient. Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
High risk	26	48	74
Standard risk	56	108	164
Unknlown	72	156	228
Stratification Factor: International Staging System (ISS) Stage per IxRS			
The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group (a lower stage indicates less progressed disease): Stage I: β2-microglobulin (β2M) < 3.5 mg/L, albumin >= 3.5 g/dL Stage II: β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin Stage III: β2M ≥ 5.5 mg/L. Higher stages indicate more advanced disease and/or poorer prognosis. Data is the ISS result assessed at the time of randomization using an interactive voice/web response system (IxRS). Reported for the Intent to Treat Population.			
Units: Subjects			
Stage I or II	127	252	379
Stage III	27	60	87
Stratification Factor: Lines of Prior Treatment per IxRS			
Number of participants grouped by total number of prior regimens. Data reported are randomization stratification values. Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
1 prior treatment	67	133	200
> = 2 prior treatments	87	179	266
Stratification Factor: Prior Proteasome Inhibitor Treatment per IxRS			
The number of participants with prior proteasome inhibitor treatment assessed at the time of randomization per the IxRS. Data reported are randomization stratification values. Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			

Yes	139	279	418
No	15	33	48
Stratification Factor: Prior CD38 Antibody Therapy per IxRS			
The number of participants with prior CD38 antibody therapy assessed at the time of randomization per the IxRS. Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
Yes	0	1	1
No	154	311	465
Geographic Regions			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: Subjects			
North America	12	21	33
Europe	103	207	310
Asia Pacific	39	84	123
Time from Initial Diagnosis to Randomization			
Baseline characteristics are reported for the Intent to Treat Population.			
Units: months			
arithmetic mean	44.03	47.86	
standard deviation	± 36.57	± 34.69	-

End points

End points reporting groups

Reporting group title	Kd - Carfilzomib and Dexamethasone

Reporting group description:

Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16 and at 40 mg on day 22 of all 28-day cycles.

Reporting group title	KdD - Carfilzomib, Dexamethasone and Daratumumab

Reporting group description:

Carfilzomib was administered intravenously (IV) at 20 mg/m^2 in Cycle 1: days 1 and 2; at 56 mg/m^2 in Cycle 1: days 8, 9, 15 and 16. The 56 mg/m^2 dosage was continued in Cycles 2+ on days 1, 2, 8, 9, 15 and 16. Dexamethasone was taken by IV infusion at 20 mg on Cycle 1, days 1 and 2 (in Cycles 2+, days 1 and 2 could be either oral or IV) and either orally or by IV infusion on days 8, 9, 15 and 16 and at 40 mg on day 22 of all 28-day cycles. The administration of dexamethasone was given on carfilzomib and/or daratumumab IV infusion days. Daratumumab was administered by IV at 8 mg/kg on Cycle 1: days 1 and 2; at 16 mg/kg on Cycle 1: days 8, 15 and 22, and Cycle 2: days 1, 8, 15, and 22. The 16 mg/kg dosage was continued on Cycles 3-6: days 1 and 15. The 16 mg/kg dosage was continued on Cycles 7+: day 1 only.

Primary: Progression-free Survival (PFS) as Assessed by the Independent Review Committee (PA DCO Only)

End point title	Progression-free Survival (PFS) as Assessed by the Independent Review Committee (PA DCO Only)

End point description:

Progression-free survival (PFS) was defined as the time from randomization to the earlier of disease progression or death due to any cause. Participants were evaluated for disease response and progression according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) as assessed by an Independent Review Committee (IRC). The duration of PFS was right censored for participants who met any of the following conditions: 1. no baseline/post-baseline disease assessments; 2. started a new anti myeloma therapy before documentation of progressive disease or death; 3. progressive disease or death immediately after more than 70 days without disease assessment visit or; 4. alive without documentation of disease progression before the analysis trigger date (PA DCO); 5. lost to follow-up or withdrawn consent.

Intent to Treat Population.

End point type	Primary

End point timeframe:

From randomization until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: participants				
Participants with PFS events	68	110		
Participants who were censored	86	202		

Statistical analyses

Statistical analysis title	KD vs KdD

Statistical analysis description:

Stratification factors used in the Log-rank p-value (1-sided) and the Cox model hazard ratio (KdD/Kd) were as assessed at randomization: International Staging System stage at screening (Stage 1 or 2 vs Stage 3); prior proteasome inhibitor exposure (yes vs no); number of prior lines of therapy (1 vs >= 2).

Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0014 [1]
Method	Logrank
Parameter estimate	Stratified Cox model hazard ratio
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.464
upper limit	0.854

Notes:

[1] - alpha level of 0.025

Secondary: Overall Response (OR) as Assessed by the Independent Review Committee (PA DCO Only)

End point title	Overall Response (OR) as Assessed by the Independent Review Committee (PA DCO Only)

End point description:

Overall response rate was defined as the percentage of participants in each treatment group who achieve partial response (PR) or better per the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) as their best response.

Complete Response (CR): No immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow.

Very Good Partial Response (VGPR): Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-component with urine M-component <100 mg/24 hours.

Partial Response (PR): ≥ 50% reduction of serum M-protein and reduction in urine M-protein by ≥ 90% or to < 200 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.

95% CIs for proportions were estimated using the Clopper-Pearson method.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

From randomization until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)	74.7 (67.0 to 81.3)	84.3 (79.8 to 88.1)		

Statistical analyses

Statistical analysis title	KD vs KdD
Statistical analysis description:	
Odds ratios and corresponding 95% CIs were estimated using the stratified Mantel-Haenszel method. P-values were calculated using the stratified Cochran-Mantel-Haenszel Chi-Square test.	
Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.925
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.184
upper limit	3.129

Secondary: Minimal Residual Disease Negative Complete Response Rate (MRD[-]CR) at 12 Months as Assessed by the Independent Review Committee

End point title	Minimal Residual Disease Negative Complete Response Rate (MRD[-]CR) at 12 Months as Assessed by the Independent Review Committee
End point description:	
MRD[-]CR at 12 months was defined as achievement of CR per IMWG-URC by IRC and MRD[-] status as assessed by next-generation sequencing (NGS; at a 10^-5 level) at the 12 months landmark (8 to 13 month window). Intent to Treat Population.	
End point type	Secondary
End point timeframe:	
12 Months (8- to 13-month window)	

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)	1.9 (0.4 to 5.6)	12.8 (9.3 to 17.0)		

Statistical analyses

Statistical analysis title	KD vs KdD

Statistical analysis description:

Odds ratios and corresponding 95% CIs were estimated using the stratified Mantel-Haenszel method.

Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	7.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.364
upper limit	25.858

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from randomization until death from any cause. Deaths collected via public source, after end of study were included. Medians were estimated using the Kaplan-Meier method. 95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. Participants still alive were censored at the date last known to be alive. 9999: not enough events to estimate the upper 95% CI.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

Up to 58 months after the first participant was enrolled (at FA DCO, a median of 40.29 weeks of treatment [any study drug] in the Kd group and 79.29 weeks of treatment [any study drug] in the KdB group; FA DCO was 15 Apr 2022)

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: months				
median (confidence interval 95%)	43.6 (35.3 to 9999)	50.8 (44.7 to 9999)		

Statistical analyses

Statistical analysis title	KD vs KdD

Statistical analysis description:

Hazard ratio and corresponding 95% CIs were estimated using the stratified Cox proportional hazards models. 1-sided p-value from the log-rank test controlling for the randomization stratification factors.

Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0417
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.784
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	1.033

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

Treatment-emergent adverse events are defined as any adverse event with an onset after the administration of the first dose of any study treatment and within the end of study or 30 days of the last dose of any study treatment, whichever occurs earlier.
The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, where Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening; Grade 5 = Fatal.

Treatment-related adverse events are treatment-emergent adverse events considered related to at least one study drug by the investigator, including those with unknown relationship.

9999999: not relevant for this treatment arm.

Safety Population.

End point type	Secondary

End point timeframe:

PA DCO: the longest treatment duration as of the PA DCO was 102.3 weeks; FA DCO: the longest treatment duration as of the FA DCO was 236.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	308		
Units: participants				
PA DCO: All TEAEs	147	306		
PA DCO: TEAEs: Severity Grade >=3	113	253		
PA DCO: TEAEs: Serious Adverse Events	70	173		
PA DCO: TEAEs: Leading to discon of carfilzomib	33	65		
PA DCO: TEAEs: Leading to discon of daratumumab	9999999	28		
PA DCO: TEAEs: Leading to discon of dexamethasone	37	33		
PA DCO: Fatal TEAEs	8	30		
PA DCO: Treatment-related TEAEs	129	260		
PA DCO: Related TEAEs: Grade >=3	74	187		
PA DCO: Related and serious TEAEs	32	84		
PA DCO: Related TEAEs: discon of carfilzomib	21	50		
PA DCO: Related TEAEs: discon of daratumumab	9999999	15		
PA DCO: Related TEAEs: discon of dexamethasone	24	19		
PA DCO: Related Fatal TEAEs	0	5		
FA DCO: All TEAEs	149	306		
FA DCO: TEAEs: Severity Grade >=3	120	273		
FA DCO: TEAEs: Serious Adverse Events	80	211		
FA DCO: TEAEs: Leading to discon of carfilzomib	37	98		
FA DCO: TEAEs: Leading to discon of daratumumab	9999999	43		
FA DCO: TEAEs: Leading to discon of dexamethasone	40	58		
FA DCO: Fatal TEAEs	11	39		
FA DCO: Treatment-related TEAEs	131	267		
FA DCO: Related TEAEs: Grade >=3	82	206		
FA DCO: Related and serious TEAEs	34	102		
FA DCO: Related TEAEs: discon of carfilzomib	22	69		
FA DCO: Related TEAEs: discon of daratumumab	9999999	18		
FA DCO: Related TEAEs: discon of dexamethasone	24	30		
FA DCO: Related Fatal TEAEs	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate for Time to Next Treatment (TTNT)

End point title	Kaplan-Meier Estimate for Time to Next Treatment (TTNT)

End point description:

Time to next treatment was defined as the time (in months) from randomization to the initiation of subsequent non-protocol anti-cancer treatment for multiple myeloma. Time to next treatment for participants who do not start the subsequent treatment for multiple myeloma was censored at the date when the participant's information was last available.

Medians of TTNT duration were estimated using the Kaplan-Meier method. 95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

99999: not enough events to estimate a median and confidence intervals yet.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

PA DCO: the longest treatment duration as of the PA DCO was 102.3 weeks; FA DCO: the longest treatment duration as of the FA DCO was 236.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: months				
median (confidence interval 95%)				
PA DCO	17.3 (13.5 to 99999)	99999 (99999 to 99999)		
FA DCO	17.8 (13.5 to 23.1)	37.4 (30.1 to 47.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate for Duration of Response (DOR) (PA DCO Only)

End point title	Kaplan-Meier Estimate for Duration of Response (DOR) (PA DCO Only)

End point description:

Duration of response (DOR) was defined as the time (in months) from first evidence of partial response (PR) or better per IMWG-URC by IRC to the earlier of disease progression or death due to any cause for participants with a best response of PR or better. For those who are alive and have not experienced disease progression at the time of data cutoff for analysis, duration of response was right-censored.

Medians were estimated using the Kaplan-Meier method. 95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

99999: not enough events to estimate a median and confidence intervals yet.

Participants who responded in the Intent to Treat Population.

End point type	Secondary

End point timeframe:

From Day 1 until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	263		
Units: months				
median (confidence interval 95%)	16.6 (13.9 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Time to Progression (TTP) as Assessed by the Independent Review Committee (PA DCO Only)

End point title	Kaplan-Meier Estimates for Time to Progression (TTP) as Assessed by the Independent Review Committee (PA DCO Only)

End point description:

Time to progression was defined as the time (in months) from randomization to documented disease progression. Participants who did not have documented disease progression were censored at the date when data was last available.

99999: not enough events to estimate a median and confidence intervals yet.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

From randomization until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: months				
median (confidence interval 95%)	17.5 (13.2 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP): Percentage of Participants Who Had Not Had Disease Progression as Assessed by the Independent Review Committee at Months 3, 6, 12, and 18 (PA DCO Only)

End point title	Time to Progression (TTP): Percentage of Participants Who Had Not Had Disease Progression as Assessed by the Independent Review Committee at Months 3, 6, 12, and 18 (PA DCO Only)

End point description:

Time to progression was defined as the time (in months) from randomization to documented disease progression. This outcome reports TTP as the percentage of participants who were event free (that is, they had not had disease progression) at the specified time frames. Independent Review Committee assessment for this outcome measure was not planned after the primary analysis.

95% CIs for event-free rates were estimated using the method by Kalbfleisch and Prentice (1980) with log-log transformation.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

Randomization to Months 3, 6, 12, and 18

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)				
3 months	90.0 (83.7 to 93.9)	95.3 (92.1 to 97.2)		
6 months	79.4 (71.6 to 85.3)	86.4 (81.8 to 89.9)		
12 months	62.7 (53.6 to 70.5)	77.5 (72.1 to 82.0)		
18 months	45.1 (34.5 to 55.4)	68.5 (62.2 to 74.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Overall Response as Assessed by the Independent Review Committee (PA DCO Only)

End point title	Time to Overall Response as Assessed by the Independent Review Committee (PA DCO Only)

End point description:

Time to overall response was defined as the time from randomization to the earliest date a response of partial response (PR) or better as per IMWG-URC is first achieved and subsequently confirmed for participants with a best response of PR or better.

Participants who responded in the Intent to Treat Population.

End point type	Secondary

End point timeframe:

From randomization until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	263		
Units: months				
arithmetic mean (standard deviation)	1.5 (± 1.1)	1.4 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved and Maintained a Minimal Residual Disease Negative Complete Response (MRD[-]CR) for 12 Months or More

End point title	Percentage of Participants Who Achieved and Maintained a Minimal Residual Disease Negative Complete Response (MRD[-]CR) for 12 Months or More

End point description:

A measure of the persistence of the CR (includes strict CR) per International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) and MRD[-] status as assessed by NGS (at a 10^-5 level) for 12 months or more after achieving MRD[-]CR status.

95% confidence intervals (CIs) for proportions were estimated using the Clopper-Pearson method.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

PA DCO: the longest treatment duration as of the PA DCO was 102.3 weeks; FA DCO: the longest treatment duration as of the FA DCO was 236.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)				
PA DCO	0.0 (0.0 to 2.4)	0.0 (0.0 to 1.2)		
FA DCO	0.0 (0.0 to 2.4)	5.8 (3.5 to 9.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Complete Response (CR) as Assessed by the Independent Review Committee (PA DCO Only)

End point title	Percentage of Participants with a Complete Response (CR) as Assessed by the Independent Review Committee (PA DCO Only)

End point description:

The percentage of participants in each treatment group who achieved stringent complete response (sCR) or CR per IMWG-URC, as assessed by the IRC, as their best response is presented.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

From randomization until the PA DCO date of 14 July 2019; the longest treatment duration as of the DCO was 102.3 weeks

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)	10.4 (6.1 to 16.3)	28.5 (23.6 to 33.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Minimal Residual Disease Negative (MRD[-]) Status as Assessed by Next Generation Sequencing at 12 Months

End point title	Percentage of Participants Who Achieved Minimal Residual Disease Negative (MRD[-]) Status as Assessed by Next Generation Sequencing at 12 Months

End point description:

MRD[-] at 12-month was defined as achievement of MRD[-] status as assessed by NGS (at a 10^-5 level) at the 12 months landmark (from 8 months to 13 months window).
95% confidence intervals (CIs) for proportions were estimated using the Clopper-Pearson method.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

12 Months (8- to 13-month window)

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: percentage of participants				
number (confidence interval 95%)	5.2 (2.3 to 10.0)	18.3 (14.1 to 23.0)		

Statistical analyses

Statistical analysis title	KD vs KdD

Statistical analysis description:

Odds ratios and corresponding 95% CIs were estimated by a stratified analysis using the Mantel-Haenszel method.

Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab

Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	4.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.007
upper limit	9.656

Secondary: Quality of Life Core Module (QLQ-C30) Global Health Status/Quality of Life Scores For Baseline Up to the First Follow-Up Visit After the Last Dose

End point title	Quality of Life Core Module (QLQ-C30) Global Health Status/Quality of Life Scores For Baseline Up to the First Follow-Up Visit After the Last Dose

End point description:

Health-related quality of life was assessed with the use of the European Organization for Research and Treatment of Cancer Quality of Life Core Module (QLQ-C30) questionnaire, a validated instrument in multiple myeloma patients. Scores range from 0 to 100, with higher scores indicating better health related quality of life.

QLQ-C30 questionnaire was administered prior to dosing every 28 ± 7 days starting from cycle 1 day 1 through first follow-up visit (30 days [+3] after last dose of all study drugs).

999999: N = 0.

Intent to Treat Population.

End point type	Secondary

End point timeframe:

Baseline (Day 1 pre-dose) up to 236.3 weeks (longest treatment duration as of the FA DCO)

End point values	Kd - Carfilzomib and Dexamethasone	KdD - Carfilzomib, Dexamethasone and Daratumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	312		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 139; 289)	66.19 (± 19.19)	61.79 (± 20.37)		
Cycle 2 (N = 126; 281)	64.35 (± 16.25)	61.00 (± 19.65)		
Cycle 3 (N = 124; 264)	66.13 (± 18.12)	63.10 (± 18.24)		
Cycle 4 (N = 112; 258)	66.67 (± 15.01)	63.47 (± 18.66)		
Cycle 5 (N = 105; 252)	67.62 (± 17.19)	64.45 (± 16.76)		
Cycle 6 (N = 96; 244)	68.06 (± 15.80)	65.92 (± 16.85)		

Cycle 7 (N = 94; 223)	69.33 (± 14.68)	65.73 (± 16.59)		
Cycle 8 (N = 87; 206)	69.44 (± 17.82)	66.34 (± 16.64)		
Cycle 9 (N = 79; 202)	65.72 (± 15.90)	67.82 (± 15.53)		
Cycle 10 (N = 73; 197)	68.38 (± 14.56)	67.98 (± 16.26)		
Cycle 11 (N = 66; 189)	67.42 (± 15.24)	68.52 (± 17.37)		
Cycle 12 (N = 65; 187)	65.13 (± 14.94)	67.47 (± 17.16)		
Cycle 13 (N = 61; 175)	67.49 (± 16.51)	67.00 (± 18.21)		
Cycle 14 (N = 59; 169)	67.66 (± 17.03)	66.12 (± 16.60)		
Cycle 15 (N = 53; 167)	69.34 (± 15.31)	67.61 (± 17.68)		
Cycle 16 (N = 54; 165)	68.21 (± 16.44)	66.41 (± 18.69)		
Cycle 17 (N = 54; 159)	69.44 (± 14.92)	69.81 (± 15.28)		
Cycle 18 (N = 52; 155)	66.67 (± 16.50)	66.29 (± 16.38)		
Cycle 19 (N = 47; 150)	69.68 (± 17.50)	68.00 (± 17.33)		
Cycle 20 (N = 40; 141)	71.04 (± 14.49)	66.43 (± 19.52)		
Cycle 21 (N = 39; 143)	70.94 (± 15.87)	67.42 (± 16.25)		
Cycle 22 (N = 36; 139)	68.52 (± 12.30)	67.51 (± 17.90)		
Cycle 23 (N = 35; 131)	69.52 (± 16.41)	66.67 (± 17.63)		
Cycle 24 (N = 35; 125)	68.10 (± 18.24)	68.00 (± 16.51)		
Cycle 25 (N = 33; 127)	67.93 (± 16.15)	66.21 (± 16.78)		
Cycle 26 (N = 33; 121)	70.71 (± 18.65)	66.12 (± 17.54)		
Cycle 27 (N = 29; 112)	65.23 (± 14.78)	66.52 (± 18.35)		
Cycle 28 (N = 29; 109)	63.22 (± 19.61)	67.28 (± 18.66)		
Cycle 29 (N = 25; 105)	66.67 (± 19.25)	67.22 (± 18.10)		
Cycle 30 (N = 24; 104)	67.01 (± 17.63)	67.23 (± 18.52)		
Cycle 31 (N = 24; 101)	68.06 (± 16.24)	67.33 (± 18.81)		
Cycle 32 (N = 23; 94)	66.67 (± 19.62)	67.91 (± 18.45)		
Cycle 33 (N = 23; 91)	67.75 (± 15.35)	67.95 (± 18.92)		
Cycle 34 (N = 22; 86)	68.18 (± 15.78)	69.86 (± 17.77)		
Cycle 35 (N = 22; 88)	65.91 (± 15.62)	69.51 (± 18.00)		
Cycle 36 (N = 23; 86)	63.77 (± 18.22)	68.22 (± 16.93)		
Cycle 37 (N = 20; 89)	67.50 (± 18.91)	68.63 (± 19.01)		

Cycle 38 (N = 17; 84)	65.20 (± 18.69)	69.25 (± 18.47)		
Cycle 39 (N = 17; 78)	64.71 (± 15.46)	68.38 (± 19.15)		
Cycle 40 (N = 14; 78)	58.33 (± 14.25)	67.74 (± 19.34)		
Cycle 41 (N = 14; 79)	66.07 (± 13.26)	68.46 (± 19.37)		
Cycle 42 (N = 14; 68)	63.69 (± 15.19)	67.16 (± 18.77)		
Cycle 43 (N = 15; 57)	67.22 (± 15.89)	63.30 (± 19.91)		
Cycle 44 (N = 12; 50)	61.81 (± 15.27)	65.50 (± 18.21)		
Cycle 45 (N = 9; 41)	67.59 (± 12.11)	66.87 (± 15.53)		
Cycle 46 (N = 8; 34)	64.58 (± 13.91)	67.89 (± 17.66)		
Cycle 47 (N = 4; 27)	66.67 (± 0.00)	68.52 (± 13.74)		
Cycle 48 (N = 3; 22)	61.11 (± 9.62)	68.56 (± 13.35)		
Cycle 49 (N = 3; 19)	61.11 (± 9.62)	68.42 (± 13.49)		
Cycle 50 (N = 3; 16)	61.11 (± 9.62)	68.75 (± 13.09)		
Cycle 51 (N = 3; 12)	63.89 (± 4.81)	67.36 (± 11.49)		
Cycle 52 (N = 2; 9)	54.17 (± 17.68)	62.04 (± 17.24)		
Cycle 53 (N = 0; 3)	999999 (± 999999)	61.11 (± 9.62)		
Follow-up (N = 25; 32)	61.00 (± 23.04)	59.90 (± 18.02)		

Statistical analyses

Statistical analysis title	KD vs KdD

Statistical analysis description:

Analysis was performed based on a linear mixed effects model. The model included fixed effects of treatment (all baseline responses were modeled with a dummy treatment), baseline QLQ-C30 GHS/QoL score, randomization stratification factors (ISS stage at screening (Stage 1 or 2 vs Stage 3), prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2)), interaction between treatment and time, and random effects of participant intercept and random slope of time.

Comparison groups	Kd - Carfilzomib and Dexamethasone v KdD - Carfilzomib, Dexamethasone and Daratumumab
Number of subjects included in analysis	466
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.948
Method	linear mixed effects model
Parameter estimate	Mean difference (final values)
Point estimate	-0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	2.35
Variability estimate	Standard error of the mean
Dispersion value	1.24

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs - any AEs with an onset after the administration of the first dose of any study treatment and within the end of the study or 30 days of the last dose, whichever occurred earlier. The longest treatment duration as of the FA DCO was 236.3 weeks.

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled/randomized in the study. Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	KdD 20/56 mg/m²
Reporting group description: -	
Reporting group title	Kd 20/56 mg/m²

Reporting group description: -

Serious adverse events	KdD 20/56 mg/m²	Kd 20/56 mg/m²	
Total subjects affected by serious adverse events			
subjects affected / exposed	211 / 308 (68.51%)	80 / 153 (52.29%)	
number of deaths (all causes)	145	79	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	8 / 308 (2.60%)	5 / 153 (3.27%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 2	
Basal cell carcinoma			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor venous access			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	3 / 308 (0.97%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 308 (0.32%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dialysis hypotension			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Unevaluable event			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	14 / 308 (4.55%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	12 / 19	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (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			
Epistaxis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 308 (2.27%)	5 / 153 (3.27%)	
occurrences causally related to treatment / all	4 / 8	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 308 (0.97%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	5 / 308 (1.62%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 308 (2.27%)	5 / 153 (3.27%)	
occurrences causally related to treatment / all	5 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary arterial hypertension			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	4 / 308 (1.30%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomania			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin abnormal			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 308 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous injury			
subjects affected / exposed	0 / 308 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dural tear			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 308 (1.30%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	1 / 308 (0.32%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 308 (1.62%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 308 (1.30%)	4 / 153 (2.61%)	
occurrences causally related to treatment / all	2 / 4	5 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 308 (0.65%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	4 / 308 (1.30%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microvascular coronary artery disease			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial enlargement			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 308 (2.60%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	3 / 10	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 308 (1.62%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	2 / 308 (0.65%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytosis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	9 / 308 (2.92%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	6 / 10	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 308 (2.60%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	10 / 308 (3.25%)	7 / 153 (4.58%)	
occurrences causally related to treatment / all	4 / 12	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 308 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonic urinary bladder			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
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			
Osteonecrosis of jaw			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 308 (0.97%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter infection			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	6 / 308 (1.95%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	14 / 308 (4.55%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	5 / 15	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			

subjects affected / exposed	7 / 308 (2.27%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 308 (0.32%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Picornavirus infection			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 308 (0.00%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	52 / 308 (16.88%)	16 / 153 (10.46%)	
occurrences causally related to treatment / all	24 / 73	7 / 17	
deaths causally related to treatment / all	1 / 5	0 / 0	
Respiratory tract infection			
subjects affected / exposed	8 / 308 (2.60%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	3 / 8	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	12 / 308 (3.90%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	6 / 15	0 / 2	
deaths causally related to treatment / all	1 / 3	0 / 2	
Septic shock			
subjects affected / exposed	5 / 308 (1.62%)	2 / 153 (1.31%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	1 / 5	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 308 (1.95%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	6 / 308 (1.95%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 308 (0.32%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	14 / 308 (4.55%)	3 / 153 (1.96%)	
occurrences causally related to treatment / all	1 / 17	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 1	
COVID-19			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic COVID-19			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes dermatitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (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 bacterial			

subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 308 (0.97%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 308 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	2 / 308 (0.65%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	1 / 308 (0.32%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	1 / 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	KdD 20/56 mg/m²	Kd 20/56 mg/m²	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	295 / 308 (95.78%)	137 / 153 (89.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	113 / 308 (36.69%)	47 / 153 (30.72%)	
occurrences (all)	246	88	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	14 / 308 (4.55%)	8 / 153 (5.23%)	
occurrences (all)	22	8	
Pyrexia			

subjects affected / exposed	57 / 308 (18.51%)	24 / 153 (15.69%)	
occurrences (all)	89	34	
Chills			
subjects affected / exposed	18 / 308 (5.84%)	7 / 153 (4.58%)	
occurrences (all)	20	7	
Asthenia			
subjects affected / exposed	35 / 308 (11.36%)	19 / 153 (12.42%)	
occurrences (all)	76	30	
Oedema peripheral			
subjects affected / exposed	38 / 308 (12.34%)	16 / 153 (10.46%)	
occurrences (all)	67	25	
Fatigue			
subjects affected / exposed	80 / 308 (25.97%)	29 / 153 (18.95%)	
occurrences (all)	159	46	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	17 / 308 (5.52%)	4 / 153 (2.61%)	
occurrences (all)	22	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 308 (17.86%)	30 / 153 (19.61%)	
occurrences (all)	75	37	
Dyspnoea			
subjects affected / exposed	68 / 308 (22.08%)	34 / 153 (22.22%)	
occurrences (all)	126	55	
Productive cough			
subjects affected / exposed	21 / 308 (6.82%)	6 / 153 (3.92%)	
occurrences (all)	39	8	
Oropharyngeal pain			
subjects affected / exposed	16 / 308 (5.19%)	4 / 153 (2.61%)	
occurrences (all)	18	6	
Epistaxis			
subjects affected / exposed	9 / 308 (2.92%)	8 / 153 (5.23%)	
occurrences (all)	9	9	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	64 / 308 (20.78%)	19 / 153 (12.42%)	
occurrences (all)	95	36	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	23 / 308 (7.47%)	3 / 153 (1.96%)	
occurrences (all)	26	4	
Contusion			
subjects affected / exposed	16 / 308 (5.19%)	2 / 153 (1.31%)	
occurrences (all)	20	2	
Fall			
subjects affected / exposed	17 / 308 (5.52%)	6 / 153 (3.92%)	
occurrences (all)	21	6	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	12 / 308 (3.90%)	8 / 153 (5.23%)	
occurrences (all)	16	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 308 (7.79%)	7 / 153 (4.58%)	
occurrences (all)	30	7	
Headache			
subjects affected / exposed	47 / 308 (15.26%)	19 / 153 (12.42%)	
occurrences (all)	88	28	
Neuropathy peripheral			
subjects affected / exposed	34 / 308 (11.04%)	6 / 153 (3.92%)	
occurrences (all)	47	14	
Peripheral sensory neuropathy			
subjects affected / exposed	26 / 308 (8.44%)	2 / 153 (1.31%)	
occurrences (all)	30	2	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	119 / 308 (38.64%)	46 / 153 (30.07%)	
occurrences (all)	495	146	
Neutropenia			

subjects affected / exposed	49 / 308 (15.91%)	15 / 153 (9.80%)	
occurrences (all)	131	28	
Lymphopenia			
subjects affected / exposed	29 / 308 (9.42%)	13 / 153 (8.50%)	
occurrences (all)	78	42	
Leukopenia			
subjects affected / exposed	21 / 308 (6.82%)	6 / 153 (3.92%)	
occurrences (all)	62	21	
Anaemia			
subjects affected / exposed	113 / 308 (36.69%)	51 / 153 (33.33%)	
occurrences (all)	325	111	
Eye disorders			
Cataract			
subjects affected / exposed	28 / 308 (9.09%)	11 / 153 (7.19%)	
occurrences (all)	33	13	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	52 / 308 (16.88%)	13 / 153 (8.50%)	
occurrences (all)	78	31	
Nausea			
subjects affected / exposed	62 / 308 (20.13%)	22 / 153 (14.38%)	
occurrences (all)	88	30	
Diarrhoea			
subjects affected / exposed	112 / 308 (36.36%)	27 / 153 (17.65%)	
occurrences (all)	200	36	
Constipation			
subjects affected / exposed	23 / 308 (7.47%)	7 / 153 (4.58%)	
occurrences (all)	27	10	
Abdominal pain			
subjects affected / exposed	13 / 308 (4.22%)	9 / 153 (5.88%)	
occurrences (all)	20	10	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	21 / 308 (6.82%)	10 / 153 (6.54%)	
occurrences (all)	29	12	
Pruritus			

subjects affected / exposed	19 / 308 (6.17%)	5 / 153 (3.27%)	
occurrences (all)	24	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 308 (11.36%)	11 / 153 (7.19%)	
occurrences (all)	60	16	
Back pain			
subjects affected / exposed	61 / 308 (19.81%)	20 / 153 (13.07%)	
occurrences (all)	90	25	
Pain in extremity			
subjects affected / exposed	25 / 308 (8.12%)	11 / 153 (7.19%)	
occurrences (all)	32	13	
Muscle spasms			
subjects affected / exposed	41 / 308 (13.31%)	19 / 153 (12.42%)	
occurrences (all)	61	27	
Musculoskeletal chest pain			
subjects affected / exposed	18 / 308 (5.84%)	6 / 153 (3.92%)	
occurrences (all)	21	6	
Muscular weakness			
subjects affected / exposed	21 / 308 (6.82%)	6 / 153 (3.92%)	
occurrences (all)	28	6	
Myalgia			
subjects affected / exposed	18 / 308 (5.84%)	4 / 153 (2.61%)	
occurrences (all)	23	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	22 / 308 (7.14%)	3 / 153 (1.96%)	
occurrences (all)	30	3	
Upper respiratory tract infection			
subjects affected / exposed	104 / 308 (33.77%)	37 / 153 (24.18%)	
occurrences (all)	277	77	
Respiratory tract infection			
subjects affected / exposed	33 / 308 (10.71%)	9 / 153 (5.88%)	
occurrences (all)	46	17	
Pneumonia			

subjects affected / exposed	38 / 308 (12.34%)	9 / 153 (5.88%)	
occurrences (all)	48	11	
Nasopharyngitis			
subjects affected / exposed	33 / 308 (10.71%)	15 / 153 (9.80%)	
occurrences (all)	67	63	
Influenza			
subjects affected / exposed	26 / 308 (8.44%)	10 / 153 (6.54%)	
occurrences (all)	29	11	
Conjunctivitis			
subjects affected / exposed	16 / 308 (5.19%)	5 / 153 (3.27%)	
occurrences (all)	18	5	
Bronchitis			
subjects affected / exposed	56 / 308 (18.18%)	21 / 153 (13.73%)	
occurrences (all)	103	26	
Sinusitis			
subjects affected / exposed	16 / 308 (5.19%)	5 / 153 (3.27%)	
occurrences (all)	23	6	
Pharyngitis			
subjects affected / exposed	18 / 308 (5.84%)	4 / 153 (2.61%)	
occurrences (all)	23	6	
Lower respiratory tract infection			
subjects affected / exposed	20 / 308 (6.49%)	4 / 153 (2.61%)	
occurrences (all)	27	4	
COVID-19			
subjects affected / exposed	16 / 308 (5.19%)	3 / 153 (1.96%)	
occurrences (all)	22	4	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	23 / 308 (7.47%)	12 / 153 (7.84%)	
occurrences (all)	33	16	
Hyperglycaemia			
subjects affected / exposed	29 / 308 (9.42%)	13 / 153 (8.50%)	
occurrences (all)	59	17	
Decreased appetite			
subjects affected / exposed	27 / 308 (8.77%)	9 / 153 (5.88%)	
occurrences (all)	38	12	

Hypocalcaemia subjects affected / exposed occurrences (all)	19 / 308 (6.17%) 26	7 / 153 (4.58%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2017	- Included safety objectives and endpoints as additional secondary objectives and endpoints. - Updated and clarified the International Myeloma Working Group Uniform Response Criteria. - Added additional exclusion criteria. - Updated list of countries participating in global study.
09 June 2017	- Modified contraception language. - Modified primary and secondary endpoint analyses to include treatment-by subgroup analyses. - Clarified when confirmation of disease progression was needed.
19 April 2018	- Clarified timing of pregnancy tests before first dose of investigational product. - Clarified recommended action for congestive heart failure. - Clarified how dosing of 20 mg dexamethasone could be split in the KdD group. - Updated which laboratory assessments were to be performed at follow-up visits. - Clarified that for participants who did not complete clinical outcome assessments (COAs) on cycle 1 day1, further COAs were not collected. - Clarified that COAs were collected electronically.
17 May 2019	Added 2 interim readouts of overall survival at 36 and 48 months after the first participant enrolled, as well as, methods for the analyses and clarification of the timing of the overall survival final analysis. - Updated language for management of hepatitis B virus reactivation, safety evaluations, and dose interruption guidelines for daratumumab. - Updated dexamethasone dosing for participants who discontinued carfilzomib and for participants with steroid intolerance. - Clarified recommended carfilzomib dose modifications for congestive heart failure. - Added the collection of subsequent antimyeloma therapy in long-term follow-up.
02 October 2019	- Clarified time of clinical outcome assessment. - Clarified International Uniform Response Criteria for Multiple Myeloma.
17 March 2021	- Removed central lab disease assessments after third Interim Analysis of overall survival data cutoff. - Updated recommendations for carfilzomib dosage adjustments and/or treatment delays. - Modified daratumumab IV infusion rates. - Added precautions related to vaccinations. - Removed daratumumab pharmacokinetic and anti-drug antibody sample collection at Follow-up Visit 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported