Clinical trial results:
A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone [DRd] vs Lenalidomide and Dexamethasone [Rd] in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Summary

EudraCT number	2014-002273-11
Trial protocol	SE AT NL GB DK IE DE BE IT
Global end of trial date	02 October 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	54767414MMY3008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252172
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical registry group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical registry group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trail was to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who were not candidates for high dose chemotherapy and autologous stem cell transplant.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	89 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 52
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 312
Country: Number of subjects enrolled	United Kingdom: 67
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Sweden: 22
Country: Number of subjects enrolled	United States: 151
Worldwide total number of subjects	737
EEA total number of subjects	424

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)	8
From 65 to 84 years	704
85 years and over	25

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 737 subjects were enrolled (368 subjects in the Daratumumab + Lenalidomide + Dexamethasone [DRd] group and 369 in the Lenalidomide + Dexamethasone [Rd] group) of which 729 were treated (364 subjects in the DRd group and 365 in the Rd group) and none completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide + Dexamethasone (Rd)

Arm description:

Subjects received Lenalidomide 25 milligrams (mg) capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously (IV) once a week (QW) until disease progression or unacceptable toxicity up to 77.5 months. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by the International Myeloma Working Group [IMWG] criteria).

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle until disease progression or unacceptable toxicity.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Dexamethasone 40 mg IV QW until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received Dexamethasone 40 mg oral tablet QW until disease progression or unacceptable toxicity.

Arm title	Daratumumab + Lenalidomide + Dexamethasone (DRd)

Arm description:

Subjects received Daratumumab 16 milligrams per kilograms (mg/kg) IV QW for the first 8 weeks (cycles 1-2) and then every 2 weeks (Q2W) for 16 weeks (Cycle 3-6), then every 4 weeks (Q4W) (from

Cycle 7 and beyond) (each cycle of 28 days), Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or IV QW until disease progression or unacceptable toxicity up to 77.3 months. After implementation of Amendment 8, subjects who were ongoing with daratumumab IV treatment were given an option to switch to daratumumab subcutaneous (SC) injection on Day 1 of any cycle, as per investigator's discretion. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by IMWG criteria).

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle until disease progression or unacceptable toxicity.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Daratumumab 16 mg/kg IV QW for the first 8 weeks (cycles 1-2) and then every 2 weeks (Q2W) for 16 weeks (Cycle 3-6), then every 4 weeks (Q4W) (from Cycle 7 and beyond) (each cycle of 28 days) until disease progression or unacceptable toxicity.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Daratumumab 16 mg/kg SC QW for the first 8 weeks (cycles 1-2) and then Q2W for 16weeks (Cycle 3-6), then Q4W (from Cycle 7 and beyond) (each cycle of 28 days).

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Dexamethasone 40 mg IV QW until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received Dexamethasone 40 mg oral QW until disease progression or unacceptable toxicity.

Number of subjects in period 1	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)
Started	369	368
Treated	365	364
Completed	0	0
Not completed	369	368
Adverse event, serious fatal	218	175
Consent withdrawn by subject	20	15
Physician decision	-	1
End of data collection	122	170
Lost to follow-up	9	6
Site closure	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide + Dexamethasone (Rd)
Reporting group description:	
Subjects received Lenalidomide 25 milligrams (mg) capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously (IV) once a week (QW) until disease progression or unacceptable toxicity up to 77.5 months. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by the International Myeloma Working Group [IMWG] criteria).	
Reporting group title	Daratumumab + Lenalidomide + Dexamethasone (DRd)
Reporting group description:	
Subjects received Daratumumab 16 milligrams per kilograms (mg/kg) IV QW for the first 8 weeks (cycles 1-2) and then every 2 weeks (Q2W) for 16 weeks (Cycle 3-6), then every 4 weeks (Q4W) (from Cycle 7 and beyond) (each cycle of 28 days), Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or IV QW until disease progression or unacceptable toxicity up to 77.3 months. After implementation of Amendment 8, subjects who were ongoing with daratumumab IV treatment were given an option to switch to daratumumab subcutaneous (SC) injection on Day 1 of any cycle, as per investigator's discretion. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by IMWG criteria).	

Reporting group values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)	Total
Number of subjects	369	368	737
Age categorical			
Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
12 - 17 years	0	0	0
Adults (18 - 64 years)	4	4	8
From 65 - 84 years	349	355	704
85 years and over	16	9	25
Age continuous			
Units: years			
arithmetic mean	74.2	74.0	
standard deviation	± 5.66	± 5.44	-
Gender categorical			
Units: Subjects			
Male	195	189	384
Female	174	179	353
Stage of Disease (ISS)			
The International Staging System (ISS) consists of following 3 stages - Stage I: serum beta2-microglobulin less than (<) 3.5 milligrams per liter (mg/L) and albumin greater than or equal to (>=) 3.5 grams per 100 Milliliter (g/100 mL); Stage II: neither stage I nor stage III and Stage III: serum beta2-microglobulin >= 5.5 mg/L.			
Units: Subjects			
Stage I	103	98	201

Stage II	156	163	319
Stage III	110	107	217

Time from Multiple Myeloma (MM) diagnosis			
Time from MM diagnosis is the time from diagnosis of multiple myeloma to randomization in each treatment group.			
Units: Months			
arithmetic mean	1.3	1.4	
standard deviation	± 1.4	± 1.5	-

End points

End points reporting groups

Reporting group title	Lenalidomide + Dexamethasone (Rd)

Reporting group description:

Subjects received Lenalidomide 25 milligrams (mg) capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously (IV) once a week (QW) until disease progression or unacceptable toxicity up to 77.5 months. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by the International Myeloma Working Group [IMWG] criteria).

Reporting group title	Daratumumab + Lenalidomide + Dexamethasone (DRd)

Reporting group description:

Subjects received Daratumumab 16 milligrams per kilograms (mg/kg) IV QW for the first 8 weeks (cycles 1-2) and then every 2 weeks (Q2W) for 16 weeks (Cycle 3-6), then every 4 weeks (Q4W) (from Cycle 7 and beyond) (each cycle of 28 days), Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or IV QW until disease progression or unacceptable toxicity up to 77.3 months. After implementation of Amendment 8, subjects who were ongoing with daratumumab IV treatment were given an option to switch to daratumumab subcutaneous (SC) injection on Day 1 of any cycle, as per investigator's discretion. After completion of treatment, subjects entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by IMWG criteria).

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS: Time from date of randomization to either progressive disease (PD) or death, whichever occurred first based on computerized algorithm as per IMWG criteria. PD: An increase of 25 percent (%) from the lowest response value in one of the following: serum and urine M-component (absolute increase must be greater than or equal to [>=] 0.5 gram per deciliter [g/dL] and >=200 mg/24 hours [h] respectively); Only in subjects without measurable serum and urine M-protein levels the difference between involved and uninvolved free light chain (FLC) levels (absolute increase must be greater than [>]10 mg/dL); development of new bone lesions or soft tissue plasmacytomas or increase in size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia attributed solely to Plasma cell (PC) proliferative disorder. Intent-to-treat (ITT) population included all randomized subjects. '99999' signifies median and 95% CI was not estimable due to insufficient number of events.

End point type	Primary

End point timeframe:

From randomization (Day -3) to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or clinical cut-off (CCO) whichever occurs first (up to 3.5 years)

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Months				
median (confidence interval 95%)	31.87 (28.94 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.73

Primary: Time to Response

End point title	Time to Response[1]

End point description:

Time to first response, VGPR or better, CR or better, best response was reported for this endpoint. Time to response: time from date of randomization to first efficacy evaluation that met criteria for PR/better as their best response (PR, CR, or better) based on IMWG criteria. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If serum and urine M-protein were not measurable, a decrease of >=50% in difference between involved and uninvolved FLC levels was required in place of M-protein criteria. Based on computerized algorithm, according to IMWG response criteria, VGPR or better: proportion of subjects with a response of VGPR or better (i.e., VGPR, CR or sCR), CR or better: proportion of subjects with a response of CR or better (i.e., CR or sCR). Here, 'N'=number of subjects evaluable for this end point; 'n'= number of subjects analyzed at specified timepoints.

End point type	Primary

End point timeframe:

From randomization (Day -3) up to 6.6 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	342		
Units: Months				

median (full range (min-max))				
Time to first response (n= 301, 342)	1.05 (0.3 to 22.3)	1.05 (0.2 to 12.1)		
Time to VGPR or better (n= 210, 300)	4.70 (0.9 to 43.3)	3.01 (0.9 to 60.9)		
Time to CR or better (n=111, 188)	13.17 (2.8 to 54.6)	10.66 (1.0 to 46.7)		
Time to best response (n=301, 342)	6.31 (0.9 to 55.2)	9.97 (0.9 to 60.9)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Percentage of subjects with a CR or better (CR or stringent complete response [sCR]) based on computerized algorithm as per IMWG criteria was reported. CR was defined as negative immunofixation on the serum and urine, and disappearance of any soft tissue plasmacytomas, and less than (<) 5 percent (%) PCs in bone marrow. In subjects with only measurable disease by serum FLC levels a normal serum FLC ratio was required. sCR was defined as in addition to CR a normal FLC ratio, and absence of clonal PCs by immunohistochemistry (IHC), immunofluorescence, 2-4 color flow cytometry (FC). ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Percentage of subjects				
number (confidence interval 95%)	30.1 (25.4 to 35.0)	51.1 (45.9 to 56.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)

Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	3.3

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

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

End point description:

MRD negativity rate is defined as the percentage of subjects who had negative MRD at any time point after the date of randomization and prior to subsequent antimyeloma therapy. MRD was assessed in subjects who achieved CR or better. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Percentage of subjects				
number (confidence interval 95%)	11.1 (8.1 to 14.8)	32.1 (27.3 to 37.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.55
upper limit	5.59

Secondary: Percentage of Subjects With Very Good Partial Response (VGPR) or Better

End point title	Percentage of Subjects With Very Good Partial Response (VGPR) or Better

End point description:

VGPR or better rate was defined as the percentage of subjects who achieved VGPR or better (VGPR, CR or sCR) according to the IMWG criteria during or after the study treatment. VGPR: Serum and urine component detectable by immunofixation but not on electrophoresis, or >= 90% reduction in serum M-protein plus urine M-protein level less than (<) 100 milligram (mg) per 24 hour; CR: negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas and < 5% plasms cells (PCs) in bone marrow; sCR: CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by IHC, immunofluorescence, 2-4 color FC. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Percentage of subjects				
number (confidence interval 95%)	56.9 (51.7 to 62.0)	81.5 (77.2 to 85.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.42
upper limit	4.77

Secondary: Percentage of Subjects With Stringent Complete Response (sCR)

End point title	Percentage of Subjects With Stringent Complete Response (sCR)

End point description:

sCR as per IMWG criteria is CR plus normal free light chain (FLC) ratio and absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. CR: Negative immunofixation on the serum and urine; Disappearance of any soft tissue plasmacytomas; <5% plasma cells (PCs) in bone marrow. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Percentage of subjects				
number (confidence interval 95%)	15.7 (12.2 to 19.8)	35.6 (30.7 to 40.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	4.24

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was measured from the date of randomization to the date of the death. Median OS was estimated by using the Kaplan-Meier method. ITT population included all randomized subjects. '99999' signifies that upper limit of 95% CI was not estimable due to an insufficient number of events.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 8.7 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Months				
number (confidence interval 95%)	64.07 (55.98 to 70.80)	90.25 (80.76 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 7
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.82

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was the percentage of subjects who achieved partial response (PR) or better (PR, VGPR, CR or sCR) based on computerized algorithm as per IMWG criteria. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If serum and urine M-protein were not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels was required in place of the M-protein criteria. If present at baseline, a >=50% reduction in the size of soft tissue plasmacytomas was also required. VGPR: serum and urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours. CR: negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas and < 5% PCs in bone marrow; sCR: CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by IHC, immunofluorescence, 2-4 color FC. ITT was used.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Percentage of subjects				
number (confidence interval 95%)	81.6 (77.2 to 85.4)	92.9 (89.8 to 95.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 6
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.85
upper limit	4.86

Secondary: Time to Disease Progression (TTP)

End point title	Time to Disease Progression (TTP)

End point description:

TTP was defined as the time from the date of randomization to date of first documented evidence of PD or death due to PD, whichever occurred first. PD per IMWG criteria- Increase of 25 % from lowest response value in one of following: Serum M-component (absolute increase >=0.5 g/dL); Urine M-component (absolute increase >=200 mg/24 hours); Only in subjects without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase >10 milligram per deciliter [mg/dL]); Definite development of new bone lesions/soft tissue plasmacytomas or definite increase in size of existing bone lesions/soft tissue plasmacytomas and Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder. ITT population included all randomized subjects. Here '99999' signifies median, upper and lower limit of 95% CI was not estimable due to an insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Months				
median (confidence interval 95%)	40.87 (35.81 to 48.79)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 8
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.62

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR was defined for subjects with confirmed response (PR or better) as time between first documentation of response and disease progression per IMWG response criteria, or death due to PD, whichever occurs first. PD per IMWG criteria- Increase of 25% from lowest response value in one of following: Serum M-component; Urine M-component; Only in subjects without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels; Definite development of new bone lesions/soft tissue plasmacytomas or definite increase in size of existing bone lesions/soft tissue plasmacytomas and Development of hypercalcemia that can be attributed solely to the PC proliferative disorder. Response evaluable population were used. Here '99999' signifies median, upper and lower of 95% CI was not estimable due to an insufficient number of subjects with events. Here, 'N' (Overall number of subjects analyzed) signifies number of subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	119		
Units: Months				
median (confidence interval 95%)	43.7 (36.8 to 52.6)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Subsequent Anti-myeloma Treatment

End point title	Time to Subsequent Anti-myeloma Treatment

End point description:

Time to subsequent anti-myeloma treatment was defined as the time from randomization to the start of subsequent anti-myeloma treatment. Kaplan-Meier method was used for the analysis. Here '99999' signifies median and upper limit of 95% CI was not estimable due to an insufficient number of subjects with events. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 8.7 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Months				

median (confidence interval 95%)	42.4 (33.5 to 50.6)	99999 (84.1 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 9
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.63

Secondary: Progression-free Survival on Next Line of Therapy (PFS2)

End point title	Progression-free Survival on Next Line of Therapy (PFS2)

End point description:

PFS2 was defined as the time from randomization to progression on next line of therapy or death, whichever comes first. Disease progression on next line of treatment was based on investigator judgment. ITT population included all randomized subjects. Here '99999' signifies upper limit of 95% CI was not estimable due to an insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	369	368		
Units: Months				
median (confidence interval 95%)	48.89 (44.09 to 56.57)	73.72 (73.72 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 10
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	737
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.76

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Global Health Status (GHS) Score

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Global Health Status (GHS) Score

End point description:

EORTC QLQ-C30 is 30 items self-reporting questionnaire, with 1 week recall period, resulting in 5 functional scales (physical, role, emotional , cognitive and social functioning), 1 GHS scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Questionnaire included 28 items with 4-point Likert type responses from "1-not at all" to "4-very much" to assess functioning and symptoms. Scores were transformed to 0 to 100 scale, with higher scores representing better GHS, better functioning, and more symptoms. Negative change from baseline values showed deterioration in quality of life or functioning and reduction in symptom and positive values indicated improvement and worsening of symptoms. ITT was used. Here 'N' signifies number of subjects who were evaluable in this endpoint; 'n' signifies number of subjects analyzed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day -24) and Day 1 of Cycles 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60 and 66 (each Cycle of 28 days)

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	314		
Units: Score on scale				
least squares mean (confidence interval 95%)				
Cycle 3 Day 1 (n= 295, 314)	1.4 (-0.7 to 3.5)	3.8 (1.7 to 5.8)		

Cycle 6 Day 1 (n= 267, 304)	4.8 (2.6 to 7)	6.3 (4.3 to 8.4)		
Cycle 9 Day 1 (n= 229, 278)	5.7 (3.4 to 8)	7.5 (5.4 to 9.7)		
Cycle 12 Day 1 (n= 231, 274)	4.5 (2.2 to 6.8)	7.8 (5.6 to 9.9)		
Cycle 18 Day 1 (n= 186, 253)	4.7 (2.2 to 7.2)	6.4 (4.1 to 8.6)		
Cycle 24 Day 1 (n= 161, 238)	4.7 (2.1 to 7.4)	6.3 (4.1 to 8.6)		
Cycle 30 Day 1 (n= 140, 213)	4.5 (1.7 to 7.3)	5.5 (3.1 to 7.9)		
Cycle 36 Day 1 (n= 119, 207)	5 (2 to 8)	7.7 (5.3 to 10.1)		
Cycle 42 Day 1 (n= 100, 184)	3.8 (0.6 to 7)	5.6 (3.1 to 8.1)		
Cycle 48 Day 1 (n= 80, 170)	3.4 (-0.1 to 6.9)	4.2 (1.6 to 6.7)		
Cycle 54 Day 1 (n= 64, 145)	6.1 (2.2 to 9.9)	4.8 (2 to 7.5)		
Cycle 60 Day 1 (n=46, 114)	4.9 (0.4 to 9.4)	4.1 (1.1 to 7.1)		
Cycle 66 Day 1 (n= 26, 78)	7.1 (1.3 to 12.8)	7.7 (4.2 to 11.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 11; Cycle 3 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0986
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	5.2

Statistical analysis title	Statistical Analysis 12, Cycle 6 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3042
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	4.4

Statistical analysis title	Statistical Analysis 13 ; Cycle 9 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2339
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	4.9

Statistical analysis title	Statistical Analysis 14; Cycle 12 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	6.3

Statistical analysis title	Statistical Analysis 15; Cycle 18 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)

Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3093
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.9

Statistical analysis title	Statistical Analysis 16; Cycle 24 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3481
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	5

Statistical analysis title	Statistical Analysis 17; Cycle 30 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5825
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	4.6

Statistical analysis title	Statistical Analysis 21; Cycle 54 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5793
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	3.3

Statistical analysis title	Statistical Analysis 18; Cycle 36 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1566
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	6.4

Statistical analysis title	Statistical Analysis 19; Cycle 42 Day 1
Comparison groups	Daratumumab + Lenalidomide + Dexamethasone (DRd) v Lenalidomide + Dexamethasone (Rd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3858
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	5.7

Statistical analysis title	Statistical Analysis 20; Cycle 48 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7296
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	5

Statistical analysis title	Statistical Analysis 22; Cycle 60 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7756
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	4.5

Statistical analysis title	Statistical Analysis 23; Cycle 66 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8458
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	7.4

Secondary: Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS)

End point title	Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS)

End point description:

EQ-5D-5L is a standardized, subject-rated questionnaire to assess health-related quality of life. The EQ-5D-5L includes 2 components: the EQ-5D-5L health state profile (descriptive system) and the EQ-5D-5L Visual Analog Scale. The Visual Analogue Scale is designed to rate the subject's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. ITT population included all randomized subjects. Here 'N' (overall number of subjects analyzed) signifies number of subjects who were evaluable in this endpoint; 'n' (number analyzed) signifies number of subjects analyzed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day -24) and Day 1 of Cycles 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60 and 66 (each Cycle of 28 days)

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	301		
Units: Score on scale				
least squares mean (confidence interval 95%)				
Cycle 3 Day 1 (n= 286, 301)	2.1 (0.3 to 4)	4.2 (2.3 to 6)		
Cycle 6 Day 1 (n= 252, 287)	4.8 (2.8 to 6.8)	7.6 (5.8 to 9.5)		
Cycle 9 Day 1 (n= 221, 267)	7 (5 to 9.1)	9.6 (7.7 to 11.5)		
Cycle 12 Day 1 (n= 227, 261)	3.6 (1.6 to 5.7)	9.4 (7.4 to 11.3)		
Cycle 18 Day 1 (n= 180, 242)	5.4 (3.2 to 7.6)	7.4 (5.4 to 9.4)		
Cycle 24 Day 1 (n=154, 227)	4.3 (2 to 6.7)	7 (5 to 9)		
Cycle 30 Day 1 (n= 133, 198)	4.6 (2.1 to 7)	6.9 (4.8 to 9.1)		
Cycle 36 Day 1 (n= 115, 195)	4.9 (2.3 to 7.5)	8.1 (6 to 10.2)		
Cycle 42 Day 1 (n= 99, 178)	4.6 (1.8 to 7.3)	5.6 (3.4 to 7.8)		
Cycle 48 Day 1 (n= 79, 162)	5.5 (2.4 to 8.5)	6.7 (4.5 to 9)		
Cycle 54 Day 1 (n= 64, 141)	3.4 (0.1 to 6.7)	5.8 (3.4 to 8.2)		
Cycle 60 Day 1 (n= 44, 112)	5.8 (1.9 to 9.6)	5.2 (2.6 to 7.8)		
Cycle 66 Day 1 (n= 26, 74)	6.9 (2 to 11.8)	5.6 (2.5 to 8.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 25; Cycle 6 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0336
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.4

Statistical analysis title	Statistical Analysis 24; Cycle 3 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1176
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	4.5

Statistical analysis title	Statistical Analysis 28; Cycle 18 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)

Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1805
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	4.8

Statistical analysis title	Statistical Analysis 29; Cycle 24 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0783
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	5.7

Statistical analysis title	Statistical Analysis 27; Cycle 12 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	8.5

Statistical analysis title	Statistical Analysis 26; Cycle 9 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0653
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	5.3

Statistical analysis title	Statistical Analysis 30; Cycle 30 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1422
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.5

Statistical analysis title	Statistical Analysis 31; Cycle 36 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0575
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	6.5

Statistical analysis title	Statistical Analysis 32; Cycle 42 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5339
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	4.5

Statistical analysis title	Statistical Analysis 33; Cycle 48 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5015
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	5

Statistical analysis title	Statistical Analysis 34; Cycle 54 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2512
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	6.3

Statistical analysis title	Statistical Analysis 35; Cycle 60 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8246
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	4.1

Statistical analysis title	Statistical Analysis 36; Cycle 66 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.664
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	4.5

Secondary: Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Utility Score

End point title	Change From Baseline in EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) Utility Score

End point description:

EQ-5D-5L is standardized, subject-reported questionnaire to assess health-related QoL. It includes 2 components: EQ-5D-5L health state profile (descriptive system) and EQ-5D-5L VAS. EQ-5D-5L

descriptive system provides a profile of subject's health state 5 dimensions (5D): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. Responses to 5D scores were combined and converted into single preference-weighted health utility index score 0 (0.0- worst health state) to 1 (1.0- better health state) representing the general health status of individual (but allows for values less than 0 by United kingdom [UK] scoring algorithm). ITT was used. Here 'N' signifies number of subjects who were evaluable in this endpoint; 'n' signifies number of subjects analyzed at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline (Day -24) and Day 1 of Cycles 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60 and 66 (each Cycle of 28 days)

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	302		
Units: Score on scale				
least squares mean (confidence interval 95%)				
Cycle 3 Day 1 (n= 286, 302)	0.081 (0.058 to 0.103)	0.097 (0.074 to 0.119)		
Cycle 6 Day 1 (n= 252, 287)	0.111 (0.087 to 0.135)	0.13 (0.107 to 0.152)		
Cycle 9 Day 1 (n= 221, 267)	0.113 (0.088 to 0.138)	0.124 (0.101 to 0.147)		
Cycle 12 Day 1 (n= 227, 261)	0.103 (0.078 to 0.128)	0.132 (0.108 to 0.155)		
Cycle 18 Day 1 (n= 180, 242)	0.089 (0.062 to 0.116)	0.116 (0.092 to 0.14)		
Cycle 24 Day 1 (n=154, 227)	0.088 (0.059 to 0.116)	0.121 (0.096 to 0.145)		
Cycle 30 Day 1 (n= 133, 198)	0.088 (0.058 to 0.118)	0.102 (0.076 to 0.127)		
Cycle 36 Day 1 (n= 115, 195)	0.099 (0.067 to 0.131)	0.109 (0.083 to 0.135)		
Cycle 42 Day 1 (n= 99, 178)	0.062 (0.028 to 0.096)	0.113 (0.086 to 0.14)		
Cycle 48 Day 1 (n=79, 162)	0.075 (0.038 to 0.112)	0.082 (0.055 to 0.11)		
Cycle 54 Day 1 (n= 64, 141)	0.05 (0.01 to 0.091)	0.087 (0.058 to 0.116)		
Cycle 60 Day 1 (n= 44, 112)	0.068 (0.02 to 0.115)	0.079 (0.047 to 0.111)		
Cycle 66 Day 1 (n= 26, 74)	0.041 (-0.019 to 0.102)	0.111 (0.073 to 0.148)		

Statistical analyses

Statistical analysis title	Statistical Analysis 38; Cycle 6 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)

Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2472
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.05

Statistical analysis title	Statistical Analysis 37; Cycle 3 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3069
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.046

Statistical analysis title	Statistical Analysis 41; Cycle 18 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1296
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.062

Statistical analysis title	Statistical Analysis 42; Cycle 24 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0762
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.07

Statistical analysis title	Statistical Analysis 40; Cycle 12 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0841
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.062

Statistical analysis title	Statistical Analysis 39; Cycle 9 Day 1
Statistical analysis description:	
NA	
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4972
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.044

Statistical analysis title	Statistical Analysis 43; Cycle 30 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4859
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.052

Statistical analysis title	Statistical Analysis 44; Cycle 36 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6031
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.051

Statistical analysis title	Statistical Analysis 45; Cycle 42 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)

Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0178
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.093

Statistical analysis title	Statistical Analysis 46; Cycle 48 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.053

Statistical analysis title	Statistical Analysis 47; Cycle 54 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1394
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.086

Statistical analysis title	Statistical Analysis 48; Cycle 60 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6982
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.068

Statistical analysis title	Statistical Analysis 49; Cycle 66 Day 1
Comparison groups	Lenalidomide + Dexamethasone (Rd) v Daratumumab + Lenalidomide + Dexamethasone (DRd)
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0543
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.14

Secondary: Sub-group Analysis: Progression-free Survival (PFS)

End point title	Sub-group Analysis: Progression-free Survival (PFS)

End point description:

PFS for subjects with cytogenic high risk was reported. PFS: time from date of randomization to either PD/death, whichever occurred first based on computerized algorithm per IMWG criteria. PD: An increase of 25% from lowest response value in 1 of following: serum and urine M-component (absolute increase must be >=0.5g/dL and >=200mg/24h respectively); Only in subjects without measurable serum and urine M-protein levels, difference between involved and uninvolved FLC levels (absolute >10 mg/dL); Development of new bone lesions or soft tissue plasmacytomas or increase in size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that could be attributed solely to PC proliferative disorder. High risk was defined as positive for any of del17p, t(14;16) or t(4;14) by (corrected serum calcium >11.5 mg/dL) Fluorescence In Situ Hybridization (FISH)/Karyotype. ITT was used. 'N' = number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomization (Day -3) to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or clinical cut-off (CCO) whichever occurs first (up to 3.5 years)

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	28		
Units: Months				
median (confidence interval 95%)	29.6 (15.6 to 34.5)	45.3 (18.4 to 61.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sub-group Analysis: Overall Response Rate (ORR)

End point title	Sub-group Analysis: Overall Response Rate (ORR)

End point description:

ORR for subjects with cytogenic high risk was reported. ORR: percentage of subjects who achieved PR/better per IMWG criteria. PR: >=50% reduction of serum M-protein, reduction in 24h urinary M-protein by >=90% or <200mg/24h. If serum/urine M-protein were not measurable, decrease of >=50% in difference between involved and uninvolved FLC levels was required in place of M-protein criteria. If present at baseline, >=50% reduction in size of soft tissue plasmacytomas was required. VGPR: serum/urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum and urine M-protein <100mg/24h. CR: negative immunofixation on serum/urine, Disappearance of soft tissue plasmacytomas, <5% PCs in bone marrow; sCR: CR in addition to normal FLC ratio, absence of clonal cells in bone marrow by IHC, immunofluorescence, 2-4 color FC. High risk: positive for any of del17p, t(14;16) or t(4;14) by FISH/Karyotype. ITT used. N=number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomization (Day -3) up to 6.6 years

End point values	Lenalidomide + Dexamethasone (Rd)	Daratumumab + Lenalidomide + Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: Percentage of subjects				
number (not applicable)	75.0	91.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and Other AEs: From start of treatment (Day 1) up to 6.6 years

Adverse event reporting additional description:

Serious and Other AEs: Safety population was defined as subjects who have received at least 1 administration of any study treatment (partial or complete).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Daratumumab + Lenalidomide + Dexamethasone (DRd)

Reporting group description:

Participants received Daratumumab 16 milligrams per kilograms (mg/kg) IV QW for the first 8 weeks (cycles 1-2) and then every 2 weeks (Q2W) for 16 weeks (Cycle 3-6), then every 4 weeks (Q4W) (from Cycle 7 and beyond) (each cycle of 28 days), Lenalidomide 25 mg capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or IV QW until disease progression or unacceptable toxicity up to 77.3 months. After implementation of Amendment 8, participants who were ongoing with daratumumab IV treatment were given an option to switch to daratumumab subcutaneous (SC) injection on Day 1 of any cycle, as per investigator's discretion. After completion of treatment, participants entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by IMWG criteria).

Reporting group title	Lenalidomide + Dexamethasone (Rd)

Reporting group description:

Participants received Lenalidomide 25 milligrams (mg) capsule orally daily on Day 1 through Day 21 of each 28-day cycle, Dexamethasone 40 mg orally or intravenously (IV) once a week (QW) until disease progression or unacceptable toxicity up to 77.5 months. After completion of treatment, participants entered follow-up phase and were not started on subsequent anti-myeloma therapy without confirmed disease progression (assessed by the International Myeloma Working Group [IMWG] criteria).

Serious adverse events	Daratumumab + Lenalidomide + Dexamethasone (DRd)	Lenalidomide + Dexamethasone (Rd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	287 / 364 (78.85%)	259 / 365 (70.96%)	
number of deaths (all causes)	287	259	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adrenal adenoma			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B precursor type acute leukaemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	6 / 364 (1.65%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	5 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Breast cancer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			

subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal neoplasm			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leiomyosarcoma			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucinous adenocarcinoma of appendix			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Porocarcinoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary pulmonary melanoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	7 / 364 (1.92%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	5 / 8	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin squamous cell carcinoma metastatic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vascular disorders			

Hypotension			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 364 (0.27%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	6 / 364 (1.65%)	10 / 365 (2.74%)	
occurrences causally related to treatment / all	6 / 6	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Air embolism			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteritis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	5 / 364 (1.37%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	3 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 364 (0.00%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	7 / 364 (1.92%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	2 / 364 (0.55%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malaise			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 364 (0.82%)	12 / 365 (3.29%)	
occurrences causally related to treatment / all	0 / 4	6 / 18	
deaths causally related to treatment / all	0 / 2	0 / 3	
Fatigue			
subjects affected / exposed	4 / 364 (1.10%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	20 / 364 (5.49%)	12 / 365 (3.29%)	
occurrences causally related to treatment / all	11 / 24	7 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sudden death			
subjects affected / exposed	1 / 364 (0.27%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Procedural failure			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical deconditioning			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystocele			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterocele			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	4 / 364 (1.10%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	3 / 364 (0.82%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 364 (1.65%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	3 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 364 (0.27%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	16 / 364 (4.40%)	14 / 365 (3.84%)	
occurrences causally related to treatment / all	14 / 17	14 / 14	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	6 / 364 (1.65%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	6 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Personality change			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	3 / 364 (0.82%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eating disorder			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	4 / 364 (1.10%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Agitation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radial pulse abnormal			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult blood positive			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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			
Accident			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			
subjects affected / exposed	4 / 364 (1.10%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
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	8 / 364 (2.20%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	7 / 364 (1.92%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	2 / 364 (0.55%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth fracture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Corneal dystrophy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	1 / 364 (0.27%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 364 (0.82%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	10 / 364 (2.75%)	15 / 365 (4.11%)	
occurrences causally related to treatment / all	6 / 16	8 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 364 (0.00%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 364 (0.55%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	2 / 4	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 364 (0.82%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	1 / 2	1 / 2	
Cardiac failure chronic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	5 / 364 (1.37%)	11 / 365 (3.01%)	
occurrences causally related to treatment / all	2 / 7	2 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac amyloidosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 364 (0.55%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 1	1 / 3	
Mitral valve incompetence			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	3 / 364 (0.82%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	3 / 364 (0.82%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal dyscognitive seizures			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	5 / 364 (1.37%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	4 / 6	6 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Nervous system disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	2 / 364 (0.55%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperaesthesia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	4 / 364 (1.10%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital neuralgia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 364 (1.37%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	1 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 364 (0.55%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar stroke			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	11 / 364 (3.02%)	9 / 365 (2.47%)	
occurrences causally related to treatment / all	10 / 11	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 364 (1.65%)	12 / 365 (3.29%)	
occurrences causally related to treatment / all	3 / 6	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 364 (0.82%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 364 (0.55%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness bilateral			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Blepharitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	4 / 364 (1.10%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	2 / 6	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 364 (1.37%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 364 (0.55%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	4 / 364 (1.10%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	11 / 364 (3.02%)	7 / 365 (1.92%)	
occurrences causally related to treatment / all	8 / 12	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	5 / 364 (1.37%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 364 (0.55%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	1 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	1 / 2	
Gastric ulcer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	7 / 364 (1.92%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal rupture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 364 (1.37%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis acute			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	4 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	6 / 364 (1.65%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 364 (0.82%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			

subjects affected / exposed	0 / 364 (0.00%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 364 (0.00%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	14 / 364 (3.85%)	15 / 365 (4.11%)	
occurrences causally related to treatment / all	4 / 17	9 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder neck sclerosis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder stenosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	6 / 364 (1.65%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	2 / 6	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral caruncle			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 364 (0.55%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Crystal arthropathy			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	4 / 364 (1.10%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone sequestrum			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	4 / 364 (1.10%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	14 / 364 (3.85%)	9 / 365 (2.47%)	
occurrences causally related to treatment / all	2 / 18	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	4 / 364 (1.10%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fistula			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	5 / 364 (1.37%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 364 (0.55%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 364 (1.10%)	5 / 365 (1.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal synovial cyst			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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	3 / 364 (0.82%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
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	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	15 / 364 (4.12%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	14 / 18	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	6 / 364 (1.65%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 364 (1.10%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	3 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	5 / 364 (1.37%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	3 / 5	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	7 / 364 (1.92%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	2 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 364 (0.00%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	11 / 364 (3.02%)	12 / 365 (3.29%)	
occurrences causally related to treatment / all	7 / 16	6 / 18	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	16 / 364 (4.40%)	8 / 365 (2.19%)	
occurrences causally related to treatment / all	6 / 16	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis infectious			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	68 / 364 (18.68%)	39 / 365 (10.68%)	
occurrences causally related to treatment / all	66 / 89	31 / 51	
deaths causally related to treatment / all	2 / 3	2 / 3	
Pneumonia bacterial			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nocardiosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 364 (0.82%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mycosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	11 / 364 (3.02%)	10 / 365 (2.74%)	
occurrences causally related to treatment / all	5 / 11	2 / 13	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sepsis syndrome			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis staphylococcal			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic embolus			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	6 / 364 (1.65%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	4 / 7	3 / 4	
deaths causally related to treatment / all	0 / 2	1 / 1	
Skin infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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	1 / 364 (0.27%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	12 / 364 (3.30%)	7 / 365 (1.92%)	
occurrences causally related to treatment / all	6 / 16	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteritis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	4 / 8	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (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 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			

subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	2 / 364 (0.55%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 364 (0.82%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	6 / 364 (1.65%)	4 / 365 (1.10%)	
occurrences causally related to treatment / all	2 / 7	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 364 (0.82%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 364 (0.82%)	2 / 365 (0.55%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 364 (0.55%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 364 (0.27%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 364 (0.27%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			

subjects affected / exposed	1 / 364 (0.27%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 364 (0.82%)	6 / 365 (1.64%)	
occurrences causally related to treatment / all	2 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 364 (0.55%)	3 / 365 (0.82%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 364 (0.27%)	0 / 365 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 365 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daratumumab + Lenalidomide + Dexamethasone (DRd)	Lenalidomide + Dexamethasone (Rd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	362 / 364 (99.45%)	358 / 365 (98.08%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	21 / 364 (5.77%)	9 / 365 (2.47%)	
occurrences (all)	29	17	
Vascular disorders			
Haematoma			
subjects affected / exposed	31 / 364 (8.52%)	23 / 365 (6.30%)	
occurrences (all)	36	31	
Deep vein thrombosis			
subjects affected / exposed	31 / 364 (8.52%)	29 / 365 (7.95%)	
occurrences (all)	35	30	
Hypertension			
subjects affected / exposed	64 / 364 (17.58%)	31 / 365 (8.49%)	
occurrences (all)	133	51	
Hypotension			
subjects affected / exposed	41 / 364 (11.26%)	33 / 365 (9.04%)	
occurrences (all)	46	37	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	134 / 364 (36.81%)	98 / 365 (26.85%)	
occurrences (all)	261	154	
Chills			
subjects affected / exposed	49 / 364 (13.46%)	6 / 365 (1.64%)	
occurrences (all)	55	8	
Fatigue			
subjects affected / exposed	163 / 364 (44.78%)	114 / 365 (31.23%)	
occurrences (all)	370	206	
Influenza like illness			
subjects affected / exposed	21 / 364 (5.77%)	17 / 365 (4.66%)	
occurrences (all)	37	20	
Non-cardiac chest pain			

subjects affected / exposed	23 / 364 (6.32%)	21 / 365 (5.75%)	
occurrences (all)	26	26	
Peripheral swelling			
subjects affected / exposed	16 / 364 (4.40%)	24 / 365 (6.58%)	
occurrences (all)	24	32	
Pyrexia			
subjects affected / exposed	85 / 364 (23.35%)	63 / 365 (17.26%)	
occurrences (all)	122	95	
Oedema peripheral			
subjects affected / exposed	155 / 364 (42.58%)	117 / 365 (32.05%)	
occurrences (all)	300	210	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	19 / 364 (5.22%)	3 / 365 (0.82%)	
occurrences (all)	23	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	122 / 364 (33.52%)	65 / 365 (17.81%)	
occurrences (all)	207	104	
Dysphonia			
subjects affected / exposed	29 / 364 (7.97%)	19 / 365 (5.21%)	
occurrences (all)	33	22	
Dyspnoea			
subjects affected / exposed	115 / 364 (31.59%)	63 / 365 (17.26%)	
occurrences (all)	171	88	
Dyspnoea exertional			
subjects affected / exposed	29 / 364 (7.97%)	25 / 365 (6.85%)	
occurrences (all)	31	32	
Epistaxis			
subjects affected / exposed	21 / 364 (5.77%)	20 / 365 (5.48%)	
occurrences (all)	26	32	
Nasal congestion			
subjects affected / exposed	22 / 364 (6.04%)	9 / 365 (2.47%)	
occurrences (all)	22	10	
Oropharyngeal pain			

subjects affected / exposed	31 / 364 (8.52%)	10 / 365 (2.74%)	
occurrences (all)	37	16	
Productive cough			
subjects affected / exposed	23 / 364 (6.32%)	11 / 365 (3.01%)	
occurrences (all)	29	13	
Rhinorrhoea			
subjects affected / exposed	30 / 364 (8.24%)	12 / 365 (3.29%)	
occurrences (all)	32	14	
Psychiatric disorders			
Agitation			
subjects affected / exposed	19 / 364 (5.22%)	10 / 365 (2.74%)	
occurrences (all)	23	12	
Anxiety			
subjects affected / exposed	39 / 364 (10.71%)	38 / 365 (10.41%)	
occurrences (all)	51	48	
Confusional state			
subjects affected / exposed	29 / 364 (7.97%)	20 / 365 (5.48%)	
occurrences (all)	35	26	
Depression			
subjects affected / exposed	36 / 364 (9.89%)	38 / 365 (10.41%)	
occurrences (all)	42	44	
Insomnia			
subjects affected / exposed	125 / 364 (34.34%)	116 / 365 (31.78%)	
occurrences (all)	176	184	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 364 (5.77%)	15 / 365 (4.11%)	
occurrences (all)	45	20	
Blood alkaline phosphatase increased			
subjects affected / exposed	20 / 364 (5.49%)	9 / 365 (2.47%)	
occurrences (all)	37	15	
Blood creatinine increased			
subjects affected / exposed	35 / 364 (9.62%)	21 / 365 (5.75%)	
occurrences (all)	62	27	
Weight decreased			

subjects affected / exposed	112 / 364 (30.77%)	69 / 365 (18.90%)	
occurrences (all)	162	103	
Weight increased			
subjects affected / exposed	28 / 364 (7.69%)	8 / 365 (2.19%)	
occurrences (all)	34	9	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	36 / 364 (9.89%)	32 / 365 (8.77%)	
occurrences (all)	52	40	
Fall			
subjects affected / exposed	40 / 364 (10.99%)	25 / 365 (6.85%)	
occurrences (all)	63	30	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	27 / 364 (7.42%)	33 / 365 (9.04%)	
occurrences (all)	36	40	
Nervous system disorders			
Dizziness			
subjects affected / exposed	79 / 364 (21.70%)	64 / 365 (17.53%)	
occurrences (all)	112	87	
Dysgeusia			
subjects affected / exposed	28 / 364 (7.69%)	17 / 365 (4.66%)	
occurrences (all)	35	17	
Hypoaesthesia			
subjects affected / exposed	22 / 364 (6.04%)	17 / 365 (4.66%)	
occurrences (all)	30	27	
Memory impairment			
subjects affected / exposed	20 / 364 (5.49%)	11 / 365 (3.01%)	
occurrences (all)	25	14	
Paraesthesia			
subjects affected / exposed	67 / 364 (18.41%)	31 / 365 (8.49%)	
occurrences (all)	95	42	
Peripheral sensory neuropathy			
subjects affected / exposed	111 / 364 (30.49%)	66 / 365 (18.08%)	
occurrences (all)	182	101	
Sciatica			

subjects affected / exposed	26 / 364 (7.14%)	19 / 365 (5.21%)	
occurrences (all)	33	24	
Taste disorder			
subjects affected / exposed	14 / 364 (3.85%)	19 / 365 (5.21%)	
occurrences (all)	15	20	
Tremor			
subjects affected / exposed	64 / 364 (17.58%)	52 / 365 (14.25%)	
occurrences (all)	97	70	
Headache			
subjects affected / exposed	79 / 364 (21.70%)	43 / 365 (11.78%)	
occurrences (all)	127	57	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	224 / 364 (61.54%)	166 / 365 (45.48%)	
occurrences (all)	1199	707	
Lymphopenia			
subjects affected / exposed	72 / 364 (19.78%)	48 / 365 (13.15%)	
occurrences (all)	281	129	
Leukopenia			
subjects affected / exposed	73 / 364 (20.05%)	42 / 365 (11.51%)	
occurrences (all)	285	110	
Anaemia			
subjects affected / exposed	154 / 364 (42.31%)	148 / 365 (40.55%)	
occurrences (all)	498	381	
Thrombocytopenia			
subjects affected / exposed	80 / 364 (21.98%)	76 / 365 (20.82%)	
occurrences (all)	276	227	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	22 / 364 (6.04%)	19 / 365 (5.21%)	
occurrences (all)	27	26	
Eye disorders			
Vision blurred			
subjects affected / exposed	30 / 364 (8.24%)	19 / 365 (5.21%)	
occurrences (all)	32	24	
Cataract			

subjects affected / exposed	88 / 364 (24.18%)	78 / 365 (21.37%)	
occurrences (all)	109	94	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	41 / 364 (11.26%)	30 / 365 (8.22%)	
occurrences (all)	63	35	
Constipation			
subjects affected / exposed	156 / 364 (42.86%)	136 / 365 (37.26%)	
occurrences (all)	259	190	
Diarrhoea			
subjects affected / exposed	237 / 364 (65.11%)	186 / 365 (50.96%)	
occurrences (all)	683	453	
Dry mouth			
subjects affected / exposed	14 / 364 (3.85%)	21 / 365 (5.75%)	
occurrences (all)	15	22	
Dyspepsia			
subjects affected / exposed	30 / 364 (8.24%)	30 / 365 (8.22%)	
occurrences (all)	38	33	
Gastrooesophageal reflux disease			
subjects affected / exposed	23 / 364 (6.32%)	24 / 365 (6.58%)	
occurrences (all)	26	26	
Haemorrhoids			
subjects affected / exposed	19 / 364 (5.22%)	11 / 365 (3.01%)	
occurrences (all)	21	14	
Nausea			
subjects affected / exposed	132 / 364 (36.26%)	87 / 365 (23.84%)	
occurrences (all)	224	137	
Stomatitis			
subjects affected / exposed	25 / 364 (6.87%)	13 / 365 (3.56%)	
occurrences (all)	28	16	
Toothache			
subjects affected / exposed	20 / 364 (5.49%)	20 / 365 (5.48%)	
occurrences (all)	21	21	
Vomiting			
subjects affected / exposed	77 / 364 (21.15%)	48 / 365 (13.15%)	
occurrences (all)	110	65	

Abdominal pain			
subjects affected / exposed	59 / 364 (16.21%)	43 / 365 (11.78%)	
occurrences (all)	84	56	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	72 / 364 (19.78%)	70 / 365 (19.18%)	
occurrences (all)	126	89	
Pruritus			
subjects affected / exposed	41 / 364 (11.26%)	35 / 365 (9.59%)	
occurrences (all)	52	45	
Night sweats			
subjects affected / exposed	14 / 364 (3.85%)	20 / 365 (5.48%)	
occurrences (all)	18	23	
Hyperhidrosis			
subjects affected / exposed	23 / 364 (6.32%)	5 / 365 (1.37%)	
occurrences (all)	27	5	
Dry skin			
subjects affected / exposed	30 / 364 (8.24%)	20 / 365 (5.48%)	
occurrences (all)	37	26	
Erythema			
subjects affected / exposed	30 / 364 (8.24%)	22 / 365 (6.03%)	
occurrences (all)	38	25	
Rash maculo-papular			
subjects affected / exposed	23 / 364 (6.32%)	10 / 365 (2.74%)	
occurrences (all)	27	16	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	20 / 364 (5.49%)	11 / 365 (3.01%)	
occurrences (all)	22	12	
Acute kidney injury			
subjects affected / exposed	34 / 364 (9.34%)	17 / 365 (4.66%)	
occurrences (all)	44	24	
Chronic kidney disease			
subjects affected / exposed	37 / 364 (10.16%)	23 / 365 (6.30%)	
occurrences (all)	55	36	
Renal impairment			

subjects affected / exposed	34 / 364 (9.34%)	35 / 365 (9.59%)	
occurrences (all)	61	45	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	105 / 364 (28.85%)	78 / 365 (21.37%)	
occurrences (all)	173	111	
Back pain			
subjects affected / exposed	146 / 364 (40.11%)	107 / 365 (29.32%)	
occurrences (all)	208	163	
Bone pain			
subjects affected / exposed	41 / 364 (11.26%)	35 / 365 (9.59%)	
occurrences (all)	49	49	
Muscle spasms			
subjects affected / exposed	110 / 364 (30.22%)	86 / 365 (23.56%)	
occurrences (all)	162	154	
Muscular weakness			
subjects affected / exposed	38 / 364 (10.44%)	25 / 365 (6.85%)	
occurrences (all)	46	37	
Musculoskeletal chest pain			
subjects affected / exposed	39 / 364 (10.71%)	45 / 365 (12.33%)	
occurrences (all)	49	59	
Musculoskeletal pain			
subjects affected / exposed	73 / 364 (20.05%)	57 / 365 (15.62%)	
occurrences (all)	91	66	
Myalgia			
subjects affected / exposed	34 / 364 (9.34%)	28 / 365 (7.67%)	
occurrences (all)	42	35	
Neck pain			
subjects affected / exposed	31 / 364 (8.52%)	32 / 365 (8.77%)	
occurrences (all)	40	40	
Osteoarthritis			
subjects affected / exposed	29 / 364 (7.97%)	21 / 365 (5.75%)	
occurrences (all)	36	32	
Pain in extremity			

subjects affected / exposed	81 / 364 (22.25%)	59 / 365 (16.16%)	
occurrences (all)	109	85	
Infections and infestations			
Bronchitis			
subjects affected / exposed	119 / 364 (32.69%)	85 / 365 (23.29%)	
occurrences (all)	235	150	
Cystitis			
subjects affected / exposed	23 / 364 (6.32%)	10 / 365 (2.74%)	
occurrences (all)	27	12	
Gastroenteritis			
subjects affected / exposed	36 / 364 (9.89%)	22 / 365 (6.03%)	
occurrences (all)	41	27	
Influenza			
subjects affected / exposed	31 / 364 (8.52%)	22 / 365 (6.03%)	
occurrences (all)	36	22	
Lower respiratory tract infection			
subjects affected / exposed	21 / 364 (5.77%)	18 / 365 (4.93%)	
occurrences (all)	57	35	
Nasopharyngitis			
subjects affected / exposed	92 / 364 (25.27%)	66 / 365 (18.08%)	
occurrences (all)	159	104	
Pneumonia			
subjects affected / exposed	64 / 364 (17.58%)	36 / 365 (9.86%)	
occurrences (all)	76	46	
Rhinitis			
subjects affected / exposed	38 / 364 (10.44%)	23 / 365 (6.30%)	
occurrences (all)	52	36	
Sinusitis			
subjects affected / exposed	26 / 364 (7.14%)	17 / 365 (4.66%)	
occurrences (all)	34	22	
Upper respiratory tract infection			
subjects affected / exposed	93 / 364 (25.55%)	52 / 365 (14.25%)	
occurrences (all)	197	87	
Urinary tract infection			
subjects affected / exposed	76 / 364 (20.88%)	44 / 365 (12.05%)	
occurrences (all)	159	88	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	93 / 364 (25.55%)	65 / 365 (17.81%)	
occurrences (all)	126	87	
Dehydration			
subjects affected / exposed	23 / 364 (6.32%)	18 / 365 (4.93%)	
occurrences (all)	36	19	
Gout			
subjects affected / exposed	19 / 364 (5.22%)	17 / 365 (4.66%)	
occurrences (all)	24	22	
Hyperglycaemia			
subjects affected / exposed	54 / 364 (14.84%)	28 / 365 (7.67%)	
occurrences (all)	174	71	
Hyperkalaemia			
subjects affected / exposed	19 / 364 (5.22%)	10 / 365 (2.74%)	
occurrences (all)	26	10	
Hypocalcaemia			
subjects affected / exposed	59 / 364 (16.21%)	35 / 365 (9.59%)	
occurrences (all)	123	69	
Hypokalaemia			
subjects affected / exposed	98 / 364 (26.92%)	71 / 365 (19.45%)	
occurrences (all)	214	150	
Hypomagnesaemia			
subjects affected / exposed	30 / 364 (8.24%)	32 / 365 (8.77%)	
occurrences (all)	76	46	
Hyponatraemia			
subjects affected / exposed	20 / 364 (5.49%)	16 / 365 (4.38%)	
occurrences (all)	48	26	
Hypophosphataemia			
subjects affected / exposed	22 / 364 (6.04%)	10 / 365 (2.74%)	
occurrences (all)	41	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2014	The overall reason for the amendment was to make clarifications to MRD monitoring and investigator feedback was incorporated into the protocol.
13 April 2015	The overall reason for the amendment was to revise the exclusion criterion for hepatitis, based on feedback from the German PEI (Paul-Ehrlich-Institute) on a related ongoing daratumumab protocol.
26 August 2015	The overall reason for the amendment was to update the criteria for treatment discontinuation, based on feedback from the UK Medicines and Healthcare Products Regulatory Agency (MHRA).
28 August 2015	The overall reason for the amendment was to incorporate the Country specific change from from UK-1 into INT-2.
17 February 2016	The overall reason for the amendment was to incorporate feedback from the French National Ethics Committee regarding duration of contraceptive use from 4 to 3 months per Investigator's Brochure (IB) and informed consent form (ICF) risk language.
26 August 2016	The overall reason for the amendment was to make revisions to clarify blood typing assessment during the screening phase by incorporating Indirect Antiglobulin (Coombs) Testing (IAT) due to the risk of daratumumab interference with blood typing. Also, further defined the exclusion criteria for hepatitis B and C, and Human Immunodeficiency Virus (HIV).
02 November 2016	The overall reason for the amendment was to revise the timepoints for the assessment of MRD-negativity to align with newly defined International Myeloma Working Group (IMWG) categories.
14 November 2016	The overall reason for the amendment was to incorporate country specific change from UK-1 into INT-3.
22 May 2017	The overall reason for the amendment was to make revision for subjects in the DRd group to continue treatment with lenalidomide and dexamethasone until disease progression or unacceptable toxicity based on continuous lenalidomide treatment emerging as the standard of care and consistent with the approved lenalidomide prescribing information. Previous version had lenalidomide and dexamethasone stopping at 2 years in the DRd group. Two subjects in the DRd group had treatment disruption due to implementing the amendment. One subject had met the 2-year mark while waiting for Institutional Review Board (IRB) approval of the amendment and received one month of treatment with daratumumab alone. The second subject signed the ICF for amendment 4 but Rd was discontinued at the 2-year mark in error.
01 June 2017	The overall reason for the amendment was to incorporate country specific change from UK-1 into INT-4.
15 January 2019	The overall reason for the amendment was following review of data from the second interim analysis by the Independent Data Monitoring Committee (IDMC), the study was amended to allow subjects in Arm A (Rd treatment group) access to daratumumab after sponsor confirmation of progressive disease (PD) per IMWG criteria.

12 June 2019	The overall reason for the amendment was to add or modify the text for identification of HBV reactivation, testing, and management of subjects with the potential for Hepatitis B Virus (HBV) reactivation in response to identification of a new important risk (HBV reactivation).
17 January 2020	The overall reason for the amendment was to make clarifications to study conduct to align with updates in daratumumab program. Quantitative immunoglobulin testing was no longer required. Confirmation of disease progression by sponsor was no longer required, except for subjects who progress on the Rd arm and then requested subsequent therapy with daratumumab.
03 April 2020	The overall reason for the amendment was to provide flexibility for study investigators to prioritize the safety of their patients during the global Coronavirus Disease 2019 (COVID-19) pandemic, and to ensure continuity of study treatment, while limiting subjects' time spent at the study center, subjects were given the option to switch from daratumumab IV to daratumumab SC. Disease evaluations were to be performed locally per the site's standard of care.
20 July 2021	The overall reason for the amendment was to define the clinical cutoff for the updated PFS analysis which marks the start of the long-term survival follow-up during which subjects will continue to receive study treatment and will be followed for OS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported