Clinical trial results:
Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Relapsed or Refractory Multiple Myeloma

Summary

EudraCT number	2013-005525-23
Trial protocol	SE GB ES DE BE NL DK PL GR
Global end of trial date	30 September 2021

Results information

Result version number	v1 (current)
This version publication date	18 November 2023
First version publication date	18 November 2023

Trial information

Trial identification

Sponsor protocol code	54767414MMY3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02076009
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	1400 McKean Road, PO Box 776 Spring House, United States, 19477
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial 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 relapsed or refractory multiple myeloma.

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	16 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	Sweden: 31
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	United States: 36

Worldwide total number of subjects	569
EEA total number of subjects	247

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)	273
From 65 to 84 years	292
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 569 subjects were randomised, of which 564 were treated (283 in the daratumumab, lenalidomide, low-dose dexamethasone [DRd] group and 281 in the lenalidomide, low-dose dexamethasone [Rd] group). None of the subjects 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, Low-dose Dexamethasone (Rd)

Arm description:

Subjects received lenalidomide at a dose of 25 milligrams (mg) orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone at a total dose of 40 mg weekly (or 20 mg weekly for subjects greater than [>] 75 years old or with a body mass index less than [<] 18.5 kilograms per meter square [kg/m^2]).

Arm type	Active comparator
Investigational medicinal product name	Low-dose Dexamethasone (Rd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low-dose dexamethasone 40 mg weekly (or 20 mg weekly for subjects greater than [>] 75 years old or with a body mass index less than [<] 18.5 kilograms per meter square [kg/m^2]).

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 milligrams (mg) from Day 1 through Day 21 of each 28-day treatment cycle.

Arm title	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)

Arm description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as an intravenous (IV) infusion once a week during treatment cycles 1 and 2 (for 8 weeks, each 28-day cycle); every 2 weeks during treatment cycles 3 to 6 (for 16 weeks, each 28-day cycle); once only on Day 1 during treatment cycles 7 onwards (for every 4 weeks). Lenalidomide was administered at a dose of 25 mg orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone was administered at a total dose of 40 mg weekly (or 20 mg weekly for subjects >75 years old or with a body mass index < 18.5 kg/m^2).

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 from Day 1 through Day 21 of each 28-day treatment cycle.

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

Dosage and administration details:

Subjects received daratumumab 16 mg/kg once a week during treatment cycles 1 and 2 (for 8 weeks, each 28-day cycle); every 2 weeks during treatment cycles 3 to 6 (for 16 weeks, each 28-day cycle); once only on Day 1 during treatment cycles 7 onwards (for every 4 weeks).

Investigational medicinal product name	Low-dose Dexamethasone (Rd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low-dose dexamethasone 40 mg weekly (or 20 mg weekly for subjects >75 years old or with a body mass index <18.5 kg/m^2).

Number of subjects in period 1	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)
Started	283	286
Treated (Safety population)	281	283
Completed	0	0
Not completed	283	286
Adverse event, serious fatal	172	153
Consent withdrawn by subject	16	12
Physician decision	-	1
End of data collection	90	118
Lost to follow-up	4	2
Progressive disease	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide, Low-dose Dexamethasone (Rd)
Reporting group description:	
Subjects received lenalidomide at a dose of 25 milligrams (mg) orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone at a total dose of 40 mg weekly (or 20 mg weekly for subjects greater than [>] 75 years old or with a body mass index less than [<] 18.5 kilograms per meter square [kg/m^2]).	
Reporting group title	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)
Reporting group description:	
Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as an intravenous (IV) infusion once a week during treatment cycles 1 and 2 (for 8 weeks, each 28-day cycle); every 2 weeks during treatment cycles 3 to 6 (for 16 weeks, each 28-day cycle); once only on Day 1 during treatment cycles 7 onwards (for every 4 weeks). Lenalidomide was administered at a dose of 25 mg orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone was administered at a total dose of 40 mg weekly (or 20 mg weekly for subjects >75 years old or with a body mass index < 18.5 kg/m^2).	

Reporting group values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)	Total
Number of subjects	283	286	569
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	140	133	273
From 65 to 84 years	140	152	292
85 years and over	3	1	4
Title for AgeContinuous Units: years			
arithmetic mean	64.3	64.4	
standard deviation	± 8.84	± 9.03	-
Title for Gender Units: subjects			
Female	119	113	232
Male	164	173	337

End points

End points reporting groups

Reporting group title	Lenalidomide, Low-dose Dexamethasone (Rd)

Reporting group description:

Subjects received lenalidomide at a dose of 25 milligrams (mg) orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone at a total dose of 40 mg weekly (or 20 mg weekly for subjects greater than [>] 75 years old or with a body mass index less than [<] 18.5 kilograms per meter square [kg/m^2]).

Reporting group title	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)

Reporting group description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as an intravenous (IV) infusion once a week during treatment cycles 1 and 2 (for 8 weeks, each 28-day cycle); every 2 weeks during treatment cycles 3 to 6 (for 16 weeks, each 28-day cycle); once only on Day 1 during treatment cycles 7 onwards (for every 4 weeks). Lenalidomide was administered at a dose of 25 mg orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone was administered at a total dose of 40 mg weekly (or 20 mg weekly for subjects >75 years old or with a body mass index < 18.5 kg/m^2).

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)[1]

End point description:

PFS: time from randomisation to progressive disease(PD)/death. PD, any 1 criteria: >=25% increase in serum M-protein level from lowest response value, absolute increase >=0.5 gram per deciliter(g/dL); >=25% increase in 24hours(h) in urinary light chain excretion (urine M-protein) from lowest response value, absolute increase >=200mg/24h; in subjects without measurable serum and urine M-protein levels: >=25% increase in difference between involved and uninvolved free light chain levels from lowest response value and absolute increase >10 mg/dL; increase in existing bone lesions/soft tissue plasmacytomas size; development of new bone lesions/soft tissue plasmacytomas; development of hypercalcemia(corrected serum calcium >11.5mg/dL) attributed to plasma cell proliferative disorder. Intent-to-treat: subjects randomly assigned to DRd or Rd group. 99999: median, upper and lower limit of 95% CI in DRd arm and upper limit of 95% CI in Rd arm not estimable due to short follow-up by subjects.

End point type	Primary

End point timeframe:

From randomisation to either disease progression or death whichever occurs first (up to 21 months)

Notes:

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

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	286		
Units: Months				
median (confidence interval 95%)	18.43 (13.86 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression (TTP)

End point title	Time to Disease Progression (TTP)

End point description:

TTP: time from date of randomization to date of first documented PD. PD, any 1 criteria:>=25% increase in serum M-protein level from lowest response value, absolute increase >=0.5 g/dL; >=25% increase in 24h in urinary light chain excretion (urine M-protein) from lowest response value, absolute increase >=200mg/24h; in subjects without measurable serum and urine M-protein levels: >=25% increase in difference between involved and uninvolved free light chain (FLC) levels from lowest response value and absolute increase >10 mg/dL; increase in existing bone lesions/soft tissue plasmacytomas size; development of new bone lesions/soft tissue plasmacytomas; development of hypercalcemia(corrected serum calcium >11.5mg/dL) attributed to plasma cell (PC) proliferative disorder. Intent-to-treat: subjects randomly assigned to DRd or Rd group. 99999: median, upper and lower limit of 95% CI in DRd arm and upper limit of 95% CI in Rd arm not estimable due to short follow-up by subjects.

End point type	Secondary

End point timeframe:

From randomisation to disease progression (up to 21 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	286		
Units: Months				
median (confidence interval 95%)	18.43 (14.78 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Very Good Partial Response (VGPR) or Better as per International Myeloma Working Group criteria (IMWG)

End point title	Percentage of Subjects who Achieved Very Good Partial Response (VGPR) or Better as per International Myeloma Working Group criteria (IMWG)

End point description:

VGPR or better: Percentage of subjects who achieved VGPR, complete response(CR) and stringent complete response(sCR) as per IMWG. IMWG criteria: Serum and urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-protein plus urine M-protein <100mg/24h, if serum and urine M-protein are not measurable, decrease of >90% in difference between involved and uninvolved FLC levels is required in place of M-protein criteria. Additionally, >=50% reduction in size of soft tissue plasmacytomas is required at baseline; CR: Negative immunofixation on serum and urine, disappearance of soft tissue plasmacytomas, <5% PCs in bone marrow; sCR: CR and normal FLC ratio, absence of clonal PCs by immunohistochemistry, immunofluorescence or 2-4 color flow cytometry. Response-evaluable set: subjects who have confirmed diagnosis of multiple myeloma, measurable disease and must received at least 1 dose of study drug and at least 1 post baseline disease assessment.

End point type	Secondary

End point timeframe:

From randomisation to disease progression (up to 21 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	281		
Units: Percentage of subjects				
number (confidence interval 95%)	44.2 (38.3 to 50.3)	75.8 (70.4 to 80.7)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Minimal residual disease was assessed for all subjects who achieved a complete response (CR) or stringent complete response (sCR). CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and <5% PCs in bone marrow; sCR: CR and normal FLC ratio, absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4 color flow cytometry. The MRD negativity rate was defined as the percentage of subjects who had negative MRD assessment at any time point after the first dose of study drugs by evaluation of bone marrow aspirates or whole blood at 10^ minus (-) 4, 10^-5, 10^-6 threshold. ITT analysis set included all subjects who were randomly assigned to the DRd or Rd group.

End point type	Secondary

End point timeframe:

From randomisation to date of first documented evidence of PD (up to 87.5 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	286		
Units: Percentage of subjects				
number (not applicable)				
MRD negative rate (10^-4)	10.2	40.6		
MRD negative rate (10^-5)	6.7	33.2		
MRD negative rate (10^-6)	1.8	13.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was measured from the date of randomisation to the date of the subject's death. ITT analysis set included all subjects who were randomly assigned to the DRd or Rd group. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From randomisation to date of death due to any cause (up to 87.5 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	153		
Units: Months				
median (confidence interval 95%)	51.84 (43.99 to 60.02)	67.58 (53.13 to 80.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time between the date of randomisation and the first efficacy evaluation that the subject met all criteria for partial response (PR) or better. Response-evaluable set (RES) is defined as subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment.

End point type	Secondary

End point timeframe:

From randomisation up to first documented CR or PR (up to 21 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	281		
Units: Months				
median (confidence interval 95%)	1.3 (1.1 to 1.9)	1.0 (1.0 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall response rate was defined as the percentage of Subjects who achieved a partial response (PR) or better according to the International Myeloma Working Group (IMWG) criteria, during or after study treatment. IMWG criteria for PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours, if the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria, in addition to the above criteria, if present at baseline, a >=50% reduction in the size of soft tissue plasmacytomas is also required. Response-evaluable set included subjects who have a confirmed diagnosis of multiple myeloma and measurable disease and must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment.

End point type	Secondary

End point timeframe:

From randomisation to disease progression (up to 21 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	281		
Units: Percentage of subjects				
number (not applicable)	76.4	92.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: time between first documented confirmed response (PR or better) and disease progression/death due to PD, whichever occurs first. PD, any 1 criteria: >=25% increase in serum M-protein level from lowest response value, absolute increase >=0.5 g/dL; >=25% increase in 24h in urinary light chain excretion (urine M-protein) from lowest response value, absolute increase >=200mg/24h; subjects without measurable serum and urine M-protein levels: >=25% increase in difference between involved and uninvolved FLC levels from lowest response value and absolute increase >10 mg/dL; increase in size of existing and development of new bone lesions/soft tissue plasmacytomas; development of hypercalcemia (corrected serum calcium >11.5mg/dL) attributed to PC proliferative disorder. RES was evaluated. N=subjects who had PR/better response. 99999: median, upper and lower limit of 95% CI in DRd arm and upper limit of 95% CI in Rd arm not estimable due to short follow-up by subjects.

End point type	Secondary

End point timeframe:

From randomisation to the date of first documented evidence of PD (up to 21 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	261		
Units: Months				
median (confidence interval 95%)	17.4 (17.4 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Subsequent Anticancer Treatment

End point title	Time to Subsequent Anticancer Treatment

End point description:

Time to subsequent anticancer treatment was defined as the time from randomization to the start of subsequent anticancer treatment or death due to progressive disease (PD), whichever occurs first. ITT analysis set included all subjects who were randomly assigned to the DRd or Rd group, and who started subsequent anticancer therapy or died due to progressive disease, whichever occurs first.

End point type	Secondary

End point timeframe:

From randomisation to date of start of subsequent anticancer treatment or death due to PD, whichever occured first (up to 87.5 months)

End point values	Lenalidomide, Low-dose Dexamethasone (Rd)	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	138		
Units: Months				
median (confidence interval 95%)	23.1 (18.6 to 26.3)	69.3 (49.7 to 82.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation up to 30 days after last dose of study treatment (up to 87.5 months)

Adverse event reporting additional description:

Safety analysis set included all randomised subjects who had at least 1 administration of any study treatment (partial or complete). In arm daratumumab, lenalidomide, low-dose dexamethasone (DRd), 1 subject had death event who was randomised but not treated, therefore, not included in safety analysis set.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)

Reporting group description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as an intravenous (IV) infusion once a week during treatment cycles 1 and 2 (for 8 weeks, each 28-day cycle); every 2 weeks during treatment cycles 3 to 6 (for 16 weeks, each 28-day cycle); once only on Day 1 during treatment cycles 7 onwards (for every 4 weeks). Lenalidomide was administered at a dose of 25 mg orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone was administered at a total dose of 40 mg weekly (or 20 mg weekly for subjects >75 years old or with a body mass index < 18.5 kg/m^2).

Reporting group title	Lenalidomide, Low-dose Dexamethasone (Rd)

Reporting group description:

Subjects received lenalidomide at a dose of 25 milligrams (mg) orally on Day 1 through Day 21 of each 28-day treatment cycle and low-dose dexamethasone at a total dose of 40 mg weekly (or 20 mg weekly for subjects greater than [>] 75 years old or with a body mass index less than [<] 18.5 kilograms per meter square [kg/m^2]).

Serious adverse events	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)	Lenalidomide, Low-dose Dexamethasone (Rd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	205 / 283 (72.44%)	148 / 281 (52.67%)	
number of deaths (all causes)	152	175	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute monocytic leukaemia			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Adenocarcinoma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign anorectal neoplasm			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus associated lymphoproliferative disorder			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			

subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombophlebitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic infarction			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 283 (1.06%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	13 / 283 (4.59%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	5 / 17	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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			
Prostatitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
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			
Obstructive airways disorder			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 283 (1.77%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary calcification			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	12 / 283 (4.24%)	10 / 281 (3.56%)	
occurrences causally related to treatment / all	11 / 12	10 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressive symptom			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Influenza B virus test positive			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diagnostic procedure			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Acetabulum fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	4 / 283 (1.41%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve injury			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior capsule rupture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound decomposition			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 283 (0.71%)	4 / 281 (1.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 283 (1.77%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	2 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 283 (1.41%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrhythmia			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic dysfunction			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial paralysis			

subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 283 (1.77%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	3 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal nerve disorder			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 283 (1.77%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	13 / 283 (4.59%)	4 / 281 (1.42%)	
occurrences causally related to treatment / all	13 / 16	4 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperviscosity syndrome			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sideroblastic anaemia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual field defect			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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 / 283 (1.41%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 283 (2.83%)	6 / 281 (2.14%)	
occurrences causally related to treatment / all	6 / 9	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	8 / 283 (2.83%)	11 / 281 (3.91%)	
occurrences causally related to treatment / all	0 / 11	5 / 14	
deaths causally related to treatment / all	0 / 1	1 / 3	
Azotaemia			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 283 (0.35%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	1 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urethral haemorrhage			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 283 (1.06%)	6 / 281 (2.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	3 / 283 (1.06%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
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 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	10 / 283 (3.53%)	7 / 281 (2.49%)	
occurrences causally related to treatment / all	4 / 12	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brucellosis			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 283 (1.06%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 283 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 283 (1.41%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective spondylitis			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 283 (1.06%)	6 / 281 (2.14%)	
occurrences causally related to treatment / all	2 / 3	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	14 / 283 (4.95%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	9 / 16	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Legionella infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	12 / 283 (4.24%)	7 / 281 (2.49%)	
occurrences causally related to treatment / all	2 / 14	2 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis fungal			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
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 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal abscess			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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	0 / 283 (0.00%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
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 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	48 / 283 (16.96%)	32 / 281 (11.39%)	
occurrences causally related to treatment / all	41 / 71	16 / 42	
deaths causally related to treatment / all	2 / 2	0 / 3	
Pneumonia bacterial			
subjects affected / exposed	2 / 283 (0.71%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia haemophilus			

subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	7 / 283 (2.47%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	5 / 283 (1.77%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	3 / 283 (1.06%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 283 (2.47%)	8 / 281 (2.85%)	
occurrences causally related to treatment / all	6 / 9	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
Septic shock			
subjects affected / exposed	4 / 283 (1.41%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	4 / 7	0 / 2	
deaths causally related to treatment / all	2 / 4	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 283 (1.06%)	7 / 281 (2.49%)	
occurrences causally related to treatment / all	3 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 283 (2.47%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (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 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine abscess			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 283 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 283 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	2 / 283 (0.71%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	0 / 283 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 283 (1.06%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 283 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)	Lenalidomide, Low-dose Dexamethasone (Rd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	278 / 283 (98.23%)	268 / 281 (95.37%)	
Vascular disorders			
Hypotension			

subjects affected / exposed	26 / 283 (9.19%)	9 / 281 (3.20%)	
occurrences (all)	32	10	
Hypertension			
subjects affected / exposed	31 / 283 (10.95%)	22 / 281 (7.83%)	
occurrences (all)	41	24	
Haematoma			
subjects affected / exposed	15 / 283 (5.30%)	6 / 281 (2.14%)	
occurrences (all)	15	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	59 / 283 (20.85%)	47 / 281 (16.73%)	
occurrences (all)	102	73	
Chills			
subjects affected / exposed	22 / 283 (7.77%)	9 / 281 (3.20%)	
occurrences (all)	26	11	
Influenza like illness			
subjects affected / exposed	27 / 283 (9.54%)	20 / 281 (7.12%)	
occurrences (all)	49	22	
Non-cardiac chest pain			
subjects affected / exposed	18 / 283 (6.36%)	5 / 281 (1.78%)	
occurrences (all)	21	6	
Oedema peripheral			
subjects affected / exposed	72 / 283 (25.44%)	50 / 281 (17.79%)	
occurrences (all)	115	99	
Pyrexia			
subjects affected / exposed	71 / 283 (25.09%)	40 / 281 (14.23%)	
occurrences (all)	123	56	
Fatigue			
subjects affected / exposed	119 / 283 (42.05%)	87 / 281 (30.96%)	
occurrences (all)	247	158	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	18 / 283 (6.36%)	9 / 281 (3.20%)	
occurrences (all)	18	9	
Cough			

subjects affected / exposed	107 / 283 (37.81%)	43 / 281 (15.30%)	
occurrences (all)	211	74	
Dyspnoea			
subjects affected / exposed	65 / 283 (22.97%)	39 / 281 (13.88%)	
occurrences (all)	107	59	
Dyspnoea exertional			
subjects affected / exposed	21 / 283 (7.42%)	11 / 281 (3.91%)	
occurrences (all)	30	14	
Epistaxis			
subjects affected / exposed	11 / 283 (3.89%)	15 / 281 (5.34%)	
occurrences (all)	13	18	
Nasal congestion			
subjects affected / exposed	23 / 283 (8.13%)	7 / 281 (2.49%)	
occurrences (all)	31	9	
Oropharyngeal pain			
subjects affected / exposed	23 / 283 (8.13%)	17 / 281 (6.05%)	
occurrences (all)	25	21	
Productive cough			
subjects affected / exposed	26 / 283 (9.19%)	11 / 281 (3.91%)	
occurrences (all)	46	12	
Rhinorrhoea			
subjects affected / exposed	18 / 283 (6.36%)	8 / 281 (2.85%)	
occurrences (all)	25	12	
Rhinitis allergic			
subjects affected / exposed	21 / 283 (7.42%)	4 / 281 (1.42%)	
occurrences (all)	27	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	25 / 283 (8.83%)	13 / 281 (4.63%)	
occurrences (all)	30	17	
Depression			
subjects affected / exposed	29 / 283 (10.25%)	9 / 281 (3.20%)	
occurrences (all)	35	10	
Insomnia			
subjects affected / exposed	80 / 283 (28.27%)	65 / 281 (23.13%)	
occurrences (all)	118	91	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 283 (6.71%)	14 / 281 (4.98%)	
occurrences (all)	36	34	
Blood creatinine increased			
subjects affected / exposed	16 / 283 (5.65%)	17 / 281 (6.05%)	
occurrences (all)	36	25	
Weight decreased			
subjects affected / exposed	31 / 283 (10.95%)	13 / 281 (4.63%)	
occurrences (all)	40	17	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	25 / 283 (8.83%)	12 / 281 (4.27%)	
occurrences (all)	37	15	
Fall			
subjects affected / exposed	24 / 283 (8.48%)	12 / 281 (4.27%)	
occurrences (all)	40	21	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	16 / 283 (5.65%)	2 / 281 (0.71%)	
occurrences (all)	18	2	
Atrial fibrillation			
subjects affected / exposed	17 / 283 (6.01%)	9 / 281 (3.20%)	
occurrences (all)	21	11	
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 283 (19.79%)	23 / 281 (8.19%)	
occurrences (all)	80	28	
Hypoaesthesia			
subjects affected / exposed	18 / 283 (6.36%)	9 / 281 (3.20%)	
occurrences (all)	25	17	
Neuropathy peripheral			
subjects affected / exposed	25 / 283 (8.83%)	18 / 281 (6.41%)	
occurrences (all)	38	25	
Paraesthesia			

subjects affected / exposed	17 / 283 (6.01%)	12 / 281 (4.27%)	
occurrences (all)	24	22	
Peripheral sensory neuropathy			
subjects affected / exposed	40 / 283 (14.13%)	27 / 281 (9.61%)	
occurrences (all)	64	43	
Tremor			
subjects affected / exposed	28 / 283 (9.89%)	26 / 281 (9.25%)	
occurrences (all)	35	29	
Dizziness			
subjects affected / exposed	35 / 283 (12.37%)	30 / 281 (10.68%)	
occurrences (all)	46	39	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	29 / 283 (10.25%)	23 / 281 (8.19%)	
occurrences (all)	208	89	
Anaemia			
subjects affected / exposed	118 / 283 (41.70%)	117 / 281 (41.64%)	
occurrences (all)	343	294	
Neutropenia			
subjects affected / exposed	185 / 283 (65.37%)	136 / 281 (48.40%)	
occurrences (all)	1035	592	
Lymphopenia			
subjects affected / exposed	20 / 283 (7.07%)	17 / 281 (6.05%)	
occurrences (all)	91	111	
Thrombocytopenia			
subjects affected / exposed	92 / 283 (32.51%)	90 / 281 (32.03%)	
occurrences (all)	372	339	
Eye disorders			
Vision blurred			
subjects affected / exposed	28 / 283 (9.89%)	17 / 281 (6.05%)	
occurrences (all)	30	18	
Cataract			
subjects affected / exposed	59 / 283 (20.85%)	35 / 281 (12.46%)	
occurrences (all)	71	41	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	30 / 283 (10.60%)	16 / 281 (5.69%)	
occurrences (all)	38	24	
Abdominal pain upper			
subjects affected / exposed	29 / 283 (10.25%)	13 / 281 (4.63%)	
occurrences (all)	42	16	
Constipation			
subjects affected / exposed	94 / 283 (33.22%)	77 / 281 (27.40%)	
occurrences (all)	151	115	
Diarrhoea			
subjects affected / exposed	169 / 283 (59.72%)	105 / 281 (37.37%)	
occurrences (all)	474	216	
Dyspepsia			
subjects affected / exposed	29 / 283 (10.25%)	9 / 281 (3.20%)	
occurrences (all)	33	11	
Nausea			
subjects affected / exposed	86 / 283 (30.39%)	53 / 281 (18.86%)	
occurrences (all)	146	67	
Stomatitis			
subjects affected / exposed	19 / 283 (6.71%)	6 / 281 (2.14%)	
occurrences (all)	25	7	
Toothache			
subjects affected / exposed	17 / 283 (6.01%)	10 / 281 (3.56%)	
occurrences (all)	22	11	
Vomiting			
subjects affected / exposed	65 / 283 (22.97%)	19 / 281 (6.76%)	
occurrences (all)	99	26	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	25 / 283 (8.83%)	10 / 281 (3.56%)	
occurrences (all)	32	13	
Pruritus			
subjects affected / exposed	34 / 283 (12.01%)	31 / 281 (11.03%)	
occurrences (all)	42	34	
Rash			

subjects affected / exposed	51 / 283 (18.02%)	36 / 281 (12.81%)	
occurrences (all)	65	48	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	33 / 283 (11.66%)	15 / 281 (5.34%)	
occurrences (all)	49	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	75 / 283 (26.50%)	55 / 281 (19.57%)	
occurrences (all)	133	85	
Back pain			
subjects affected / exposed	76 / 283 (26.86%)	56 / 281 (19.93%)	
occurrences (all)	124	86	
Bone pain			
subjects affected / exposed	29 / 283 (10.25%)	16 / 281 (5.69%)	
occurrences (all)	37	18	
Muscle spasms			
subjects affected / exposed	87 / 283 (30.74%)	61 / 281 (21.71%)	
occurrences (all)	128	106	
Myalgia			
subjects affected / exposed	22 / 283 (7.77%)	17 / 281 (6.05%)	
occurrences (all)	25	25	
Musculoskeletal chest pain			
subjects affected / exposed	32 / 283 (11.31%)	24 / 281 (8.54%)	
occurrences (all)	38	26	
Muscular weakness			
subjects affected / exposed	29 / 283 (10.25%)	26 / 281 (9.25%)	
occurrences (all)	49	35	
Pain in extremity			
subjects affected / exposed	47 / 283 (16.61%)	42 / 281 (14.95%)	
occurrences (all)	64	56	
Neck pain			
subjects affected / exposed	22 / 283 (7.77%)	13 / 281 (4.63%)	
occurrences (all)	28	16	
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	30 / 283 (10.60%)	26 / 281 (9.25%)	
occurrences (all)	62	37	
Bronchitis			
subjects affected / exposed	60 / 283 (21.20%)	45 / 281 (16.01%)	
occurrences (all)	112	66	
Conjunctivitis			
subjects affected / exposed	19 / 283 (6.71%)	6 / 281 (2.14%)	
occurrences (all)	22	8	
Gastroenteritis			
subjects affected / exposed	25 / 283 (8.83%)	9 / 281 (3.20%)	
occurrences (all)	35	9	
Influenza			
subjects affected / exposed	34 / 283 (12.01%)	17 / 281 (6.05%)	
occurrences (all)	38	19	
Lower respiratory tract infection			
subjects affected / exposed	22 / 283 (7.77%)	12 / 281 (4.27%)	
occurrences (all)	49	24	
Nasopharyngitis			
subjects affected / exposed	100 / 283 (35.34%)	62 / 281 (22.06%)	
occurrences (all)	279	118	
Pneumonia			
subjects affected / exposed	51 / 283 (18.02%)	27 / 281 (9.61%)	
occurrences (all)	80	34	
Respiratory tract infection			
subjects affected / exposed	38 / 283 (13.43%)	29 / 281 (10.32%)	
occurrences (all)	73	49	
Rhinitis			
subjects affected / exposed	23 / 283 (8.13%)	5 / 281 (1.78%)	
occurrences (all)	37	7	
Sinusitis			
subjects affected / exposed	27 / 283 (9.54%)	13 / 281 (4.63%)	
occurrences (all)	42	19	
Upper respiratory tract infection			
subjects affected / exposed	123 / 283 (43.46%)	74 / 281 (26.33%)	
occurrences (all)	330	147	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	50 / 283 (17.67%)	36 / 281 (12.81%)	
occurrences (all)	81	50	
Hyperglycaemia			
subjects affected / exposed	34 / 283 (12.01%)	22 / 281 (7.83%)	
occurrences (all)	78	35	
Hypocalcaemia			
subjects affected / exposed	24 / 283 (8.48%)	16 / 281 (5.69%)	
occurrences (all)	46	20	
Hypokalaemia			
subjects affected / exposed	58 / 283 (20.49%)	35 / 281 (12.46%)	
occurrences (all)	118	77	
Hypomagnesaemia			
subjects affected / exposed	18 / 283 (6.36%)	17 / 281 (6.05%)	
occurrences (all)	26	22	
Hypophosphataemia			
subjects affected / exposed	22 / 283 (7.77%)	14 / 281 (4.98%)	
occurrences (all)	68	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2014	The overall reason for this amendment was 1) The sample size was changed to reflect the median progression-free survival (PFS) assumption for the comparator arm; 2) Lenalidomide global pregnancy prevention plan was added; Feedback from investigators and health authorities was incorporated.
20 November 2014	The overall reason for this amendment was 1) The requirements for bone marrow sample collection were modified to allow for differences across countries in local clinical practice; 2) Other protocol procedures were clarified based on feedback from investigative sites; 3) Changes from France (FRA)-1 and Japan (JPN)-1 amendments were rolled into the global interim (INT)-2 amendment.
26 May 2016	The overall reason for the amendment was to include that following the positive interim analysis of efficacy results, subjects who were randomized to the Rd group and who had sponsor-confirmed disease progression were offered treatment with daratumumab monotherapy. Subjects who received daratumumab monotherapy had a limited schedule of assessments and limited adverse event (AE) collection.
01 November 2016	The overall reason for the amendment was to include additional time points for collection of bone marrow aspirate, for purposes of minimal residual disease (MRD) assessment, to align with newly defined categories of MRD-negativity.
22 January 2018	The overall reason for the amendment was to allow disease evaluations to be performed by the central laboratory on the current schedule until median PFS was reached in the daratumumab, lenalidomide, and low-dose dexamethasone (DRd) arm of the randomized portion of the study, for uniformity in data analysis. Thereafter, disease evaluations for all subjects were performed by local laboratories according to each site's standard of care. In addition, patient reported outcome (PRO) assessments were collected for an extended duration intended to ensure optimal evaluation of long-term health-related quality of life parameters.
05 December 2018	The overall reason for the amendment was to include changes in response to identification of a new important risk (Hepatitis B Virus reactivation).
12 June 2019	The overall reason for the amendment was to align guidance on monitoring and management of Hepatitis B Virus reactivation with other daratumumab studies.
09 April 2020	The overall reason for the amendment was to include changes to provide flexibility for study investigators to prioritize the safety of their patients during the global COVID-19 pandemic. To ensure continuity of study treatment, while limiting subjects' time spent at the study center, subjects who were receiving daratumumab intravenous (16 milligrams per kilogram [mg/kg]) were given the option to switch to daratumumab subcutaneous (SC) (1800 mg) on Day 1 of any cycle, at the discretion of the investigator. Assessments to evaluate the immunogenicity of recombinant human hyaluronidase PH20 (rHuPH20) were added as part of this protocol amendment.
06 April 2021	The overall reason for the amendment was to clarify that sites would be notified of the clinical cutoff (CCO) for the final overall survival (OS) analysis, to define the end of the electronic case report form (eCRF) data collection, to amend the end of study, and to clarify that subjects who were benefiting from study treatment would be able to continue to receive study treatment from the final OS analysis until the end of study when alternative access to daratumumab was not available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported