Clinical trial results:
versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma. CheckMate 743: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743

Summary

EudraCT number	2016-001859-43
Trial protocol	GR NL BE DE FR PL GB IT
Global end of trial date	28 April 2023

Results information

Result version number	v1 (current)
This version publication date	10 May 2024
First version publication date	10 May 2024

Trial information

Trial identification

Sponsor protocol code	CA209-743

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	14 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate efficacy of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in subjects with unresectable malignant pleural mesothelioma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2016
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: 33
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Colombia: 16
Country: Number of subjects enrolled	France: 102
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 61
Country: Number of subjects enrolled	Japan: 60
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Türkiye: 14
Country: Number of subjects enrolled	United Kingdom: 38

Country: Number of subjects enrolled	United States: 59
Worldwide total number of subjects	605
EEA total number of subjects	293

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)	167
From 65 to 84 years	432
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

605 participants randomized and 584 treated.

Period 1

Period 1 title	Pre-treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A

Arm description:

Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg Q2W

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg Q6W

Arm title	Treatment B

Arm description:

Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles

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

Dosage and administration details:

as a 10-minute dose of 500 mg/m² on Day 1 of a q 21 day cycle

Investigational medicinal product name	Carboplatin Area Under the Curve (AUC) 5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: Day 1 of every 21 days per cycle for 6 cycles.	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m²	

Number of subjects in period 1	Treatment A	Treatment B
Started	303	302
Completed	300	284
Not completed	3	18
Participant withdrew consent	1	11
Not reported	-	1
Participant no longer meets study criteria	2	3
Participant request to discontinue study treatment	-	3

Period 2	
Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Treatment A
Arm description: Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W	
Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1 mg/kg Q6W	
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Infusion

Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg Q2W

Arm title	Treatment B

Arm description:

Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles

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

Dosage and administration details:

as a 10-minute dose of 500 mg/m² on Day 1 of a q 21 day cycle

Investigational medicinal product name	Carboplatin Area Under the Curve (AUC) 5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Day 1 of every 21 days per cycle for 6 cycles.

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

Dosage and administration details:

75 mg/m²

Number of subjects in period 2	Treatment A	Treatment B
Started	300	284
Completed	0	189
Not completed	300	95
Administrative reason by Sponsor	2	-
Participant withdrew consent	6	3
Not reported	7	-
Maximum Clinical Benefit	11	2
Participant no longer meets study criteria	4	-
Adverse Event unrelated to Study Drug	11	9
Poor/Non-compliance	1	-
Other reasons	12	2
Study Drug Toxicity	60	24

Lost to follow-up	-	2
Disease Progression	182	43
Participant request to discontinue study treatment	4	10

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A
Reporting group description:	
Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W	
Reporting group title	Treatment B
Reporting group description:	
Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles	

Reporting group values	Treatment A	Treatment B	Total
Number of subjects	303	302	605
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	68.7	67.8	
standard deviation	± 8.5	± 9.7	-
Sex: Female, Male Units: Participants			
Female	69	69	138
Male	234	233	467
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	4	6
Asian	26	39	65
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	266	250	516
More than one race	0	0	0
Unknown or Not Reported	9	9	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	19	19	38
Not Hispanic or Latino	122	136	258
Unknown or Not Reported	162	147	309

End points

End points reporting groups	
Reporting group title	Treatment A
Reporting group description: Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W	
Reporting group title	Treatment B
Reporting group description: Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles	
Reporting group title	Treatment A
Reporting group description: Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W	
Reporting group title	Treatment B
Reporting group description: Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles	

Primary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description: Overall Survival was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive.	
End point type	Primary
End point timeframe: From randomization to the date of death (Up to 40 Months)	

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	302		
Units: Months				
median (confidence interval 95%)	18.07 (16.82 to 21.45)	14.09 (12.45 to 16.23)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio (HR)
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	605
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 [1]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74

Confidence interval	
level	Other: 96.6 %
sides	2-sided
lower limit	0.6
upper limit	0.91

Notes:

[1] - Boundary for statistical significance was a p-value < 0.0345

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate is defined as the percentage of randomized participants who achieve a best overall response of complete response (CR) or partial response (PR) per Blinded Independent Central Review (BICR) assessments. Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measureable disease and contribute to the sum that defines the pleural uni-variate measure. Per RECIST 1.1 for solid tumors, confirmation of response required:
CR=Disappearance of all target lesions;
PR=At least a 30% decrease in the sum of the Total Tumor Measurement;
Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

End point type	Secondary

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	302		
Units: Percentage of Participants				
number (confidence interval 95%)	39.3 (33.7 to 45.0)	44.4 (38.7 to 50.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease Control Rate is defined as the percentage of all randomized participants whose Best Overall Response was complete response (CR), partial response (PR), stable disease (SD) or Non-CR/Non-PD as assessed by Blinded Independent Central Review (BICR). Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measureable disease and contribute to the sum that defines the pleural uni-variate measure. Per RECIST 1.1 for solid tumors, confirmation of response required:
CR=Disappearance of all target lesions;
PR=At least a 30% decrease in the sum of the Total Tumor Measurement;
Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement;
SD=Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD;
Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

End point type	Secondary

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	302		
Units: Percentage of Participants				
number (confidence interval 95%)	76.6 (71.4 to 81.2)	85.8 (81.3 to 89.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival is defined as the time between the date of randomization and the date of first documented tumor progression per Blinded Independent Central Review (BICR) assessments (using adapted m-RECIST and RECIST 1.1), or death due to any cause, whichever occurs first. Participants who received subsequent anticancer therapy prior to documented progression were censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anticancer therapy.
Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

End point type	Secondary

End point timeframe:

From randomization date to the date of first documented tumor progression or death due to any cause, whichever occurs first. (up to 76 months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	302		
Units: Months				
median (confidence interval 95%)	6.77 (5.59 to 7.36)	7.23 (6.93 to 8.05)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio (HR)
Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	605
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.13

Secondary: Overall Survival (OS) According to PD-L1 Expression Level

End point title	Overall Survival (OS) According to PD-L1 Expression Level

End point description:

PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by overall survival (OS) analysis. OS was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive.

End point type	Secondary

End point timeframe:

From randomization date to the date of death (Up to 76 Months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	297		
Units: Months				
median (confidence interval 95%)				
<1% PD-L1	17.3 (10.1 to 23.9)	16.6 (13.4 to 20.8)		
≥1% PD-L1	18.0 (16.8 to 21.5)	13.3 (11.6 to 15.4)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio (HR)

Statistical analysis description:

<1% PD-L1

Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.32

Statistical analysis title	OS Hazard Ratio (HR)
Statistical analysis description: ≥1% PD-L1	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.88

Secondary: Progression Free Survival (PFS) According to PD-L1 Expression Level

End point title	Progression Free Survival (PFS) According to PD-L1 Expression Level

End point description:

PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by progression free survival (PFS) analysis. PFS is defined as the time between the date of randomization and the date of first documented tumor progression per Blinded Independent Central Review (BICR) assessments (using adapted m-RECIST and RECIST 1.1), or death due to any cause, whichever occurs first. Participants who received subsequent anticancer therapy prior to documented progression were censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anticancer therapy. Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

End point type	Secondary

End point timeframe:

From randomization date to the date of first documented tumor progression or death due to any cause, whichever occurs first. (up to 76 months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	297		
Units: Months				
median (confidence interval 95%)				
<1% PD-L1	4.1 (2.7 to 5.6)	8.3 (7.0 to 11.1)		
≥1% PD-L1	7.0 (5.8 to 8.5)	7.1 (6.2 to 7.6)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio (HR)
Statistical analysis description: ≥1% PD-L1	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.96

Statistical analysis title	PFS Hazard Ratio (HR)
Statistical analysis description: < 1% PD-L1	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	2.63

Secondary: Objective Response Rate (ORR) According to PD-L1 Expression Level

End point title	Objective Response Rate (ORR) According to PD-L1 Expression Level

End point description:

PD-L1 Expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression and efficacy is determined by objective response rate (ORR) analysis. ORR is defined as the percentage of participants who achieve a best overall response of complete response (CR) or partial response (PR) per Blinded Independent Central Review (BICR) assessments. Per adapted m-RECIST for pleural mesothelioma, each single tumor measurement must be at least 10 mm in length to qualify as measureable disease and contribute to the sum that defines the pleural uni-variate measure.
per RECIST 1.1 for solid tumors, confirmation of response required:
CR=Disappearance of all target lesions;
PR=At least a 30% decrease in the sum of the Total Tumor Measurement;
Progressive disease (PD)=At least a 20% increase in the sum of the Total Tumor Measurement.

End point type	Secondary

End point timeframe:

From randomization date to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to 76 months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	297		
Units: Percentage of Participants				
number (confidence interval 95%)				
<1% PD-L1	21.1 (11.4 to 33.9)	41.0 (30.0 to 52.7)		
≥1% PD-L1	43.1 (36.6 to 49.7)	45.7 (38.9 to 52.5)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Extended Collection: Overall Survival (OS)

End point title	Extended Collection: Overall Survival (OS)

End point description:

Overall Survival was defined as the time from randomization to the date of death due to any cause. A participant who has not died was censored at last known date alive.

End point type	Post-hoc

End point timeframe:

From randomization date to the date of death (Up to 76 Months)

End point values	Treatment A	Treatment B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	302		
Units: Months				
median (confidence interval 95%)	18.07 (16.82 to 20.99)	14.09 (12.45 to 16.33)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio (HR)
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	605
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.0008
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.88

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were assessed for deaths (all-causes) from their first dose to their study completion (up to approximately 76 months.) SAEs and NSAEs were assessed from first dose to 100 days post the last dose of study therapy (up to approximately 29 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Treatment B

Reporting group description:

Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin 5 AUC up to 6 cycles

Reporting group title	Treatment A

Reporting group description:

Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W

Serious adverse events	Treatment B	Treatment A	
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 284 (37.32%)	188 / 300 (62.67%)	
number of deaths (all causes)	259	251	
number of deaths resulting from adverse events	49	58	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 284 (0.70%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast neoplasm			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma malignant			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	42 / 284 (14.79%)	51 / 300 (17.00%)	
occurrences causally related to treatment / all	0 / 45	0 / 52	
deaths causally related to treatment / all	0 / 40	0 / 44	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolism			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell arteritis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 284 (0.70%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 284 (1.41%)	4 / 300 (1.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperpyrexia			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Illness			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			

subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 284 (0.35%)	4 / 300 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (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	4 / 284 (1.41%)	16 / 300 (5.33%)	
occurrences causally related to treatment / all	1 / 4	3 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related hypersensitivity reaction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	8 / 284 (2.82%)	9 / 300 (3.00%)	
occurrences causally related to treatment / all	0 / 9	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 284 (0.70%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 284 (0.35%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	3 / 284 (1.06%)	9 / 300 (3.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pleurisy			
subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 284 (0.00%)	9 / 300 (3.00%)	
occurrences causally related to treatment / all	0 / 0	7 / 10	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	2 / 284 (0.70%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 284 (1.06%)	6 / 300 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary oedema			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 284 (0.35%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Aspiration			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
General physical condition abnormal			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat exhaustion			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	0 / 284 (0.00%)	6 / 300 (2.00%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (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 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
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 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 284 (0.35%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limbic encephalitis			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis transverse			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 284 (3.17%)	5 / 300 (1.67%)	
occurrences causally related to treatment / all	11 / 16	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelosuppression			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haematotoxicity			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Opsoclonus myoclonus			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	2 / 284 (0.70%)	5 / 300 (1.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 284 (0.00%)	9 / 300 (3.00%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 284 (0.35%)	5 / 300 (1.67%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastritis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overflow diarrhoea			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (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	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior mesenteric artery dissection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 284 (0.70%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 284 (0.00%)	5 / 300 (1.67%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			

subjects affected / exposed	0 / 284 (0.00%)	5 / 300 (1.67%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
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	2 / 284 (0.70%)	7 / 300 (2.33%)	
occurrences causally related to treatment / all	0 / 2	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypophysitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			

subjects affected / exposed	0 / 284 (0.00%)	4 / 300 (1.33%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Back pain			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			

subjects affected / exposed	0 / 284 (0.00%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Candida sepsis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella urinary tract infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa fungal			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			

subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy bacterial			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 284 (2.11%)	14 / 300 (4.67%)	
occurrences causally related to treatment / all	1 / 7	0 / 14	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 284 (0.70%)	3 / 300 (1.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			

subjects affected / exposed	0 / 284 (0.00%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 284 (0.35%)	2 / 300 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 284 (0.35%)	4 / 300 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	1 / 284 (0.35%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 284 (0.70%)	0 / 300 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 300 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment B	Treatment A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	264 / 284 (92.96%)	277 / 300 (92.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 284 (2.82%)	16 / 300 (5.33%)	
occurrences (all)	8	20	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 284 (4.93%)	50 / 300 (16.67%)	
occurrences (all)	19	79	
Pain			
subjects affected / exposed	11 / 284 (3.87%)	20 / 300 (6.67%)	
occurrences (all)	14	21	
Oedema peripheral			
subjects affected / exposed	19 / 284 (6.69%)	47 / 300 (15.67%)	
occurrences (all)	19	49	
Non-cardiac chest pain			
subjects affected / exposed	16 / 284 (5.63%)	39 / 300 (13.00%)	
occurrences (all)	16	47	
Malaise			
subjects affected / exposed	17 / 284 (5.99%)	8 / 300 (2.67%)	
occurrences (all)	20	9	
Fatigue			
subjects affected / exposed	78 / 284 (27.46%)	90 / 300 (30.00%)	
occurrences (all)	96	110	
Chest pain			
subjects affected / exposed	21 / 284 (7.39%)	22 / 300 (7.33%)	
occurrences (all)	23	23	
Asthenia			
subjects affected / exposed	58 / 284 (20.42%)	52 / 300 (17.33%)	
occurrences (all)	63	74	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	25 / 284 (8.80%)	65 / 300 (21.67%)	
occurrences (all)	25	79	
Hiccups			
subjects affected / exposed	17 / 284 (5.99%)	2 / 300 (0.67%)	
occurrences (all)	28	2	
Dyspnoea			
subjects affected / exposed	41 / 284 (14.44%)	77 / 300 (25.67%)	
occurrences (all)	42	92	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 284 (5.63%)	27 / 300 (9.00%)	
occurrences (all)	17	29	
Investigations			
Weight decreased			
subjects affected / exposed	24 / 284 (8.45%)	17 / 300 (5.67%)	
occurrences (all)	25	17	
Lipase increased			
subjects affected / exposed	4 / 284 (1.41%)	27 / 300 (9.00%)	
occurrences (all)	4	42	
Blood creatinine increased			
subjects affected / exposed	19 / 284 (6.69%)	26 / 300 (8.67%)	
occurrences (all)	20	49	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 284 (1.06%)	18 / 300 (6.00%)	
occurrences (all)	3	22	
Amylase increased			
subjects affected / exposed	4 / 284 (1.41%)	24 / 300 (8.00%)	
occurrences (all)	4	36	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 284 (1.41%)	22 / 300 (7.33%)	
occurrences (all)	4	36	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 284 (0.70%)	22 / 300 (7.33%)	
occurrences (all)	2	26	

Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	15 / 284 (5.28%)	3 / 300 (1.00%)	
occurrences (all)	15	3	
Headache			
subjects affected / exposed	12 / 284 (4.23%)	24 / 300 (8.00%)	
occurrences (all)	12	28	
Dysgeusia			
subjects affected / exposed	22 / 284 (7.75%)	15 / 300 (5.00%)	
occurrences (all)	23	16	
Dizziness			
subjects affected / exposed	10 / 284 (3.52%)	16 / 300 (5.33%)	
occurrences (all)	11	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	118 / 284 (41.55%)	41 / 300 (13.67%)	
occurrences (all)	136	56	
Leukopenia			
subjects affected / exposed	25 / 284 (8.80%)	0 / 300 (0.00%)	
occurrences (all)	31	0	
Neutropenia			
subjects affected / exposed	79 / 284 (27.82%)	5 / 300 (1.67%)	
occurrences (all)	137	5	
Thrombocytopenia			
subjects affected / exposed	32 / 284 (11.27%)	5 / 300 (1.67%)	
occurrences (all)	54	6	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	19 / 284 (6.69%)	1 / 300 (0.33%)	
occurrences (all)	19	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	55 / 284 (19.37%)	47 / 300 (15.67%)	
occurrences (all)	78	56	
Nausea			
subjects affected / exposed	124 / 284 (43.66%)	76 / 300 (25.33%)	
occurrences (all)	200	95	

Diarrhoea			
subjects affected / exposed	34 / 284 (11.97%)	96 / 300 (32.00%)	
occurrences (all)	45	152	
Abdominal pain			
subjects affected / exposed	13 / 284 (4.58%)	30 / 300 (10.00%)	
occurrences (all)	15	30	
Constipation			
subjects affected / exposed	86 / 284 (30.28%)	57 / 300 (19.00%)	
occurrences (all)	104	73	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	5 / 284 (1.76%)	18 / 300 (6.00%)	
occurrences (all)	5	21	
Rash			
subjects affected / exposed	21 / 284 (7.39%)	60 / 300 (20.00%)	
occurrences (all)	23	76	
Pruritus			
subjects affected / exposed	5 / 284 (1.76%)	62 / 300 (20.67%)	
occurrences (all)	5	70	
Dry skin			
subjects affected / exposed	7 / 284 (2.46%)	16 / 300 (5.33%)	
occurrences (all)	7	16	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 284 (1.06%)	37 / 300 (12.33%)	
occurrences (all)	3	38	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 284 (3.17%)	18 / 300 (6.00%)	
occurrences (all)	9	19	
Myalgia			
subjects affected / exposed	7 / 284 (2.46%)	24 / 300 (8.00%)	
occurrences (all)	7	27	
Back pain			
subjects affected / exposed	13 / 284 (4.58%)	21 / 300 (7.00%)	
occurrences (all)	14	23	

Arthralgia subjects affected / exposed occurrences (all)	9 / 284 (3.17%) 10	49 / 300 (16.33%) 55	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 284 (2.82%) 8	21 / 300 (7.00%) 32	
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	11 / 284 (3.87%) 11	19 / 300 (6.33%) 23	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	11 / 284 (3.87%) 13	19 / 300 (6.33%) 24	
Decreased appetite subjects affected / exposed occurrences (all)	75 / 284 (26.41%) 109	72 / 300 (24.00%) 78	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2017	inclusion and exclusion criteria updated
25 April 2019	Endpoints updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported