Clinical trial results:
An Open-label, Randomized, Phase 3 Study of Nivolumab or Chemotherapy in Subjects with Relapsed Small-cell Lung Cancer after Platinum-based First Line Chemotherapy
(CheckMate 331: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 331)

Summary

EudraCT number	2015-001097-18
Trial protocol	CZ AT DE BE GB DK HU GR PL ES FR RO IT
Global end of trial date	22 August 2022

Results information

Result version number	v1 (current)
This version publication date	05 August 2023
First version publication date	05 August 2023

Trial information

Trial identification

Sponsor protocol code	CA209-331

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	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb International Corporation, EU Study Start-Up Unit, 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	11 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare efficacy of Nivolumab versus chemotherapy in subjects with relapsed small-cell lung cancer (SCLC) after platinum-based, first-line chemotherapy.

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	14 September 2015
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	Austria: 5
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	China: 82
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 13
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Romania: 32
Country: Number of subjects enrolled	Russian Federation: 15

Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	569
EEA total number of subjects	299

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)	347
From 65 to 84 years	221
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

569 randomized and 547 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	Group A

Arm description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

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

Dosage and administration details:

240mg on Day 1 of a 14-day cycle

Arm title	Group B

Arm description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

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

Dosage and administration details:

40 mg/m^2 once daily on Days 1 to 3 of a 21-day cycle

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

Dosage and administration details:

1.5 mg/m^2 IV OR 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle

Number of subjects in period 1	Group A	Group B
Started	284	285
Completed	282	265
Not completed	2	20
Consent withdrawn by subject	-	10
subject request to discontinue study treatment	-	4
Other reasons	1	1
Participant no longer meets Study Criteria	-	4
Disease Progression	1	1

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	Group A

Arm description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

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

Dosage and administration details:

240mg on Day 1 of a 14-day cycle

Arm title	Group B

Arm description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

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

Dosage and administration details:

40 mg/m^2 once daily on Days 1 to 3 of a 21-day cycle

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion, Capsule
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

1.5 mg/m^2 IV OR 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle

Number of subjects in period 2	Group A	Group B
Started	282	265
Completed	0	0
Not completed	282	265
Adverse event, serious fatal	1	1
Consent withdrawn by subject	2	3
Study drug toxicity	18	38
Adverse Event unrelated to Study drug	14	11
Maximum Clinical Benefit	-	5
subject request to discontinue study treatment	6	34
Other reasons	6	1
Lost to follow-up	1	-
Disease Progression	233	171
Administrative reason by sponsor	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Nivolumab 240mg IV on Day 1 of a 14-day cycle	
Reporting group title	Group B
Reporting group description:	
Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)	

Reporting group values	Group A	Group B	Total
Number of subjects	284	285	569
Age categorical			
Units:			
Age Continuous			
Units: years			
arithmetic mean	61.5	61.6	
standard deviation	± 9.2	± 8.4	-
Sex: Female, Male			
Units: Participants			
Female	110	108	218
Male	174	177	351
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	70	71	141
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	211	211	422
More than one race	0	0	0
Unknown or Not Reported	2	0	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	4	6	10
Not Hispanic or Latino	125	142	267
Unknown or Not Reported	155	137	292

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Nivolumab 240mg IV on Day 1 of a 14-day cycle	
Reporting group title	Group B
Reporting group description:	
Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)	
Reporting group title	Group A
Reporting group description:	
Nivolumab 240mg IV on Day 1 of a 14-day cycle	
Reporting group title	Group B
Reporting group description:	
Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 Oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
The time from randomization to the date of death, data was based on Kaplan-Meier Estimates. A participant who has not died will be censored at last known date alive.	
End point type	Primary
End point timeframe:	
OS was followed continuously while participants were on the study drug and every 3 months, minimum follow up for overall survival was 15.8 months	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Months				
median (confidence interval 95%)	7.46 (5.65 to 9.20)	8.38 (7.03 to 10.02)		

Statistical analyses

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

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1144
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.04

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of randomized participants whose best overall response (BOR) from baseline is either a complete response (CR) or partial response (PR) based on investigator assessment per RECIST 1.1 criteria. For participants without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For participants who continue nivolumab beyond progression, the BOR should be determined based on tumor assessments before initial RECIST 1.1 defined progression.
CR= Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
PR= At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)= At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

From randomization to the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (Up to approximately 80 months)

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Percentage of Participants				
number (confidence interval 95%)	13.7 (10.0 to 18.3)	16.8 (12.7 to 21.7)		

Statistical analyses

Statistical analysis title	Estimate of Odds Ratio (OR)
Comparison groups	Group A v Group B

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Estimate of Odds Ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.24

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from randomization to the date of the first documented tumor progression based on investigator assessment (per RECIST 1.1), or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.
Progressive disease (PD)= At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

From randomization to the date of first documented tumor progression, or death due to any cause. Tumor response assessed every 6 weeks from first dose until week 30, and every 12 weeks (Up to approximately 80 months)

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Months				
median (confidence interval 95%)	1.45 (1.41 to 1.51)	3.71 (2.96 to 4.24)		

Statistical analyses

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

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.66

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

End point title	Overall Survival (OS) - Extended Collection

End point description:

The time from randomization to the date of death, data was based on Kaplan-Meier Estimates. A participant who has not died will be censored at last known date alive.

End point type	Post-hoc

End point timeframe:

OS was followed continuously while participants were on the study drug and every 3 months, minimum follow up for overall survival was 64 months (Up to approximately 80 months)

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Months				
median (confidence interval 95%)	7.46 (5.65 to 9.20)	8.38 (7.03 to 10.02)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Group A v Group B
Number of subjects included in analysis	569
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs are assessed from first dose to 100 days post last dose (Up to approximately 72 months). Participants were assessed for deaths (all causes) from their first dose to study completion (Up to approximately 80 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Group B

Reporting group description:

Chemotherapy (Topotecan 1.5 mg/m^2 IV or 2.3 mg/m^2 oral once daily on Days 1 to 5 of a 21-day cycle / Amrubicin 40 mg/m^2 IV once daily on Days 1 to 3 of a 21-day cycle)

Reporting group title	Group A

Reporting group description:

Nivolumab 240mg IV on Day 1 of a 14-day cycle

Serious adverse events	Group B	Group A	
Total subjects affected by serious adverse events			
subjects affected / exposed	171 / 265 (64.53%)	183 / 282 (64.89%)	
number of deaths (all causes)	246	249	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tongue neoplasm			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottic cancer			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	85 / 265 (32.08%)	108 / 282 (38.30%)	
occurrences causally related to treatment / all	0 / 89	0 / 116	
deaths causally related to treatment / all	0 / 79	0 / 96	
Pericardial effusion malignant			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Second primary malignancy			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour invasion			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Poor venous access			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	2 / 265 (0.75%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Performance status decreased			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 265 (0.75%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Oedema peripheral			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 265 (2.26%)	8 / 282 (2.84%)	
occurrences causally related to treatment / all	1 / 8	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 4	
Fatigue			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	5 / 265 (1.89%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 265 (1.13%)	4 / 282 (1.42%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			

subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 265 (0.75%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (3.02%)	9 / 282 (3.19%)	
occurrences causally related to treatment / all	1 / 8	1 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 265 (1.13%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	2 / 265 (0.75%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (0.00%)	10 / 282 (3.55%)	
occurrences causally related to treatment / all	0 / 0	9 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 265 (1.51%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	2 / 265 (0.75%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Mediastinal disorder			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 265 (0.75%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood electrolytes abnormal			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	2 / 265 (0.75%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	10 / 265 (3.77%)	4 / 282 (1.42%)	
occurrences causally related to treatment / all	12 / 12	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 265 (0.75%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	4 / 265 (1.51%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection related reaction			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial flutter			

subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 265 (0.38%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Brain oedema			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar ataxia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 265 (0.75%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			

subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic neurological syndrome			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Seizure			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 265 (1.13%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	23 / 265 (8.68%)	7 / 282 (2.48%)	
occurrences causally related to treatment / all	25 / 25	0 / 7	
deaths causally related to treatment / all	3 / 3	0 / 1	
Bone marrow failure			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	14 / 265 (5.28%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	13 / 14	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	10 / 265 (3.77%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	11 / 265 (4.15%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	11 / 12	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancytopenia			
subjects affected / exposed	8 / 265 (3.02%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	15 / 265 (5.66%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	15 / 15	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia obstructive			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 265 (1.51%)	4 / 282 (1.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 265 (0.38%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 265 (0.38%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral disorder			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 265 (0.75%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Duodenal ulcer			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 265 (0.38%)	4 / 282 (1.42%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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			
Dermatitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic pemphigus			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder dilatation			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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	2 / 265 (0.75%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cushing's syndrome			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperthyroidism			
subjects affected / exposed	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	2 / 265 (0.75%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 265 (0.38%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 265 (0.75%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			

subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis bacterial			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous erysipelas			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
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 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (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	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	4 / 265 (1.51%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 265 (3.40%)	15 / 282 (5.32%)	
occurrences causally related to treatment / all	1 / 10	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia aspiration			

subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 265 (0.75%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 265 (0.75%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	2 / 2	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 265 (0.38%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	2 / 265 (0.75%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 265 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 265 (0.38%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	3 / 265 (1.13%)	5 / 282 (1.77%)	
occurrences causally related to treatment / all	1 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 265 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group B	Group A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 265 (93.58%)	249 / 282 (88.30%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	60 / 265 (22.64%)	65 / 282 (23.05%)	
occurrences (all)	78	76	
Fatigue			
subjects affected / exposed	78 / 265 (29.43%)	63 / 282 (22.34%)	
occurrences (all)	95	76	
Pyrexia			
subjects affected / exposed	37 / 265 (13.96%)	28 / 282 (9.93%)	
occurrences (all)	37	38	
Oedema peripheral			
subjects affected / exposed	17 / 265 (6.42%)	12 / 282 (4.26%)	
occurrences (all)	17	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 265 (19.62%)	63 / 282 (22.34%)	
occurrences (all)	60	78	
Dyspnoea			
subjects affected / exposed	45 / 265 (16.98%)	63 / 282 (22.34%)	
occurrences (all)	51	80	
Epistaxis			

subjects affected / exposed	15 / 265 (5.66%)	2 / 282 (0.71%)	
occurrences (all)	17	2	
Productive cough			
subjects affected / exposed	8 / 265 (3.02%)	20 / 282 (7.09%)	
occurrences (all)	8	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 265 (6.42%)	23 / 282 (8.16%)	
occurrences (all)	25	25	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 265 (3.40%)	16 / 282 (5.67%)	
occurrences (all)	10	25	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 265 (6.04%)	22 / 282 (7.80%)	
occurrences (all)	22	28	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 265 (4.91%)	22 / 282 (7.80%)	
occurrences (all)	14	27	
Amylase increased			
subjects affected / exposed	2 / 265 (0.75%)	15 / 282 (5.32%)	
occurrences (all)	2	19	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 265 (4.15%)	20 / 282 (7.09%)	
occurrences (all)	14	22	
Lipase increased			
subjects affected / exposed	4 / 265 (1.51%)	27 / 282 (9.57%)	
occurrences (all)	6	36	
Haemoglobin decreased			
subjects affected / exposed	14 / 265 (5.28%)	5 / 282 (1.77%)	
occurrences (all)	18	8	
Neutrophil count decreased			
subjects affected / exposed	60 / 265 (22.64%)	28 / 282 (9.93%)	
occurrences (all)	137	44	
Platelet count decreased			

subjects affected / exposed	63 / 265 (23.77%)	20 / 282 (7.09%)	
occurrences (all)	124	30	
Weight decreased			
subjects affected / exposed	16 / 265 (6.04%)	26 / 282 (9.22%)	
occurrences (all)	16	27	
White blood cell count decreased			
subjects affected / exposed	46 / 265 (17.36%)	26 / 282 (9.22%)	
occurrences (all)	123	58	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	16 / 265 (6.04%)	8 / 282 (2.84%)	
occurrences (all)	22	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	17 / 265 (6.42%)	20 / 282 (7.09%)	
occurrences (all)	17	21	
Headache			
subjects affected / exposed	21 / 265 (7.92%)	30 / 282 (10.64%)	
occurrences (all)	26	35	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	41 / 265 (15.47%)	12 / 282 (4.26%)	
occurrences (all)	114	17	
Anaemia			
subjects affected / exposed	163 / 265 (61.51%)	68 / 282 (24.11%)	
occurrences (all)	275	95	
Neutropenia			
subjects affected / exposed	93 / 265 (35.09%)	17 / 282 (6.03%)	
occurrences (all)	182	25	
Thrombocytopenia			
subjects affected / exposed	78 / 265 (29.43%)	19 / 282 (6.74%)	
occurrences (all)	188	21	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 265 (5.28%)	19 / 282 (6.74%)	
occurrences (all)	16	21	

Abdominal pain upper			
subjects affected / exposed	11 / 265 (4.15%)	16 / 282 (5.67%)	
occurrences (all)	12	17	
Stomatitis			
subjects affected / exposed	17 / 265 (6.42%)	12 / 282 (4.26%)	
occurrences (all)	24	13	
Nausea			
subjects affected / exposed	59 / 265 (22.26%)	48 / 282 (17.02%)	
occurrences (all)	85	61	
Diarrhoea			
subjects affected / exposed	44 / 265 (16.60%)	34 / 282 (12.06%)	
occurrences (all)	56	48	
Vomiting			
subjects affected / exposed	41 / 265 (15.47%)	33 / 282 (11.70%)	
occurrences (all)	59	48	
Constipation			
subjects affected / exposed	49 / 265 (18.49%)	45 / 282 (15.96%)	
occurrences (all)	59	56	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 265 (9.81%)	4 / 282 (1.42%)	
occurrences (all)	26	4	
Pruritus			
subjects affected / exposed	4 / 265 (1.51%)	27 / 282 (9.57%)	
occurrences (all)	4	43	
Rash			
subjects affected / exposed	11 / 265 (4.15%)	21 / 282 (7.45%)	
occurrences (all)	11	26	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 265 (0.38%)	23 / 282 (8.16%)	
occurrences (all)	1	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 265 (6.42%)	27 / 282 (9.57%)	
occurrences (all)	20	32	

Back pain			
subjects affected / exposed	25 / 265 (9.43%)	30 / 282 (10.64%)	
occurrences (all)	27	31	
Pain in extremity			
subjects affected / exposed	11 / 265 (4.15%)	16 / 282 (5.67%)	
occurrences (all)	11	19	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 265 (4.91%)	15 / 282 (5.32%)	
occurrences (all)	16	21	
Pneumonia			
subjects affected / exposed	22 / 265 (8.30%)	16 / 282 (5.67%)	
occurrences (all)	24	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	70 / 265 (26.42%)	79 / 282 (28.01%)	
occurrences (all)	86	93	
Hyperglycaemia			
subjects affected / exposed	8 / 265 (3.02%)	15 / 282 (5.32%)	
occurrences (all)	10	21	
Hypokalaemia			
subjects affected / exposed	18 / 265 (6.79%)	19 / 282 (6.74%)	
occurrences (all)	22	27	
Hyponatraemia			
subjects affected / exposed	25 / 265 (9.43%)	24 / 282 (8.51%)	
occurrences (all)	30	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	Study Director and Medical Monitor Updated
07 September 2016	Analysis timeline and exploratory objectives updated
20 March 2018	Study personnel updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported