



Clinical trial results:

A Single-Arm, Open-Label, Multicenter Clinical Trial with Nivolumab (BMS-936558) for Subjects with Histologically Confirmed Stage III (unresectable) or stage IV Melanoma progressing after prior treatment Containing an Anti-CTLA-4 Monoclonal Antibody.

Summary

EudraCT number	2014-001286-28
Trial protocol	BE IT DE GB ES NL AT DK PT IE SE FI HU CZ GR PL
Global end of trial date	18 January 2019

Results information

Result version number	v1 (current)
This version publication date	02 February 2020
First version publication date	02 February 2020

Trial information

Trial identification

Sponsor protocol code	CA209-172
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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	18 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main study objective is to determine the incidence of high-grade, treatment-related, select adverse events (AEs) in patients with histologically confirmed stage III (unresectable) or stage IV melanoma and progression after prior treatment containing an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody.

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 92
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Switzerland: 24
Country: Number of subjects enrolled	United Kingdom: 132
Country: Number of subjects enrolled	Austria: 37
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 196
Country: Number of subjects enrolled	Greece: 37
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Italy: 259
Country: Number of subjects enrolled	Luxembourg: 1
Country: Number of subjects enrolled	Netherlands: 40
Country: Number of subjects enrolled	Norway: 14
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Romania: 5

Country: Number of subjects enrolled	Russian Federation: 48
Worldwide total number of subjects	1009
EEA total number of subjects	937

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)	583
From 65 to 84 years	418
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1009 participants were enrolled into the study , 1008 wrere treated, 1 participants was not treated due to withdrew consent

Period 1

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

Arms

Arm title	Nivolumab 3mg/kg
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Arm description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558-01
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg

Number of subjects in period 1^[1]	Nivolumab 3mg/kg
Started	1008
Completed	1008

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1009 participants were enrolled into the study , 1008 wrere treated, 1 participants was not treated due to withdrew consent.

Baseline characteristics

Reporting groups

Reporting group title	Nivolumab 3mg/kg
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Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks

Reporting group values	Nivolumab 3mg/kg	Total	
Number of subjects	1008	1008	
Age categorical			
Units: Subjects			
Adult < 65	583	583	
Adult >= 65 and <85	417	417	
Adult >=85	8	8	
Age Continuous			
Units: years			
arithmetic mean	60.1		
standard deviation	± 13.84	-	
Sex: Female, Male			
Units: Participants			
Female	451	451	
Male	557	557	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	987	987	
More than one race	6	6	
Unknown or Not Reported	9	9	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	27	27	
Not Hispanic or Latino	972	972	
Unknown or Not Reported	9	9	

End points

End points reporting groups

Reporting group title	Nivolumab 3mg/kg
Reporting group description:	
Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks	

Primary: the Incidence of highgrade (CTCAE v4.0 Grade 3 or higher), treatment related,select adverse events.

End point title	the Incidence of highgrade (CTCAE v4.0 Grade 3 or higher), treatment related,select adverse events. ^[1]
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End point description:

The number of participants who reported high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select AEs (pulmonary,gastrointestinal, skin, renal, hepatic, endocrine) were summarized using the all treated analysis set by system organ class and Medical Dictionary for Regulatory (MedDRA) preferred term.

End point type	Primary
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End point timeframe:

Up to 2 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics were planned for this endpoint.

End point values	Nivolumab 3mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	1008			
Units: Number				
Gastrointestinal Adverse events (Grade 3-4)	17			
Gastrointestinal adverse events (Grade 5)	0			
Hepatic adverse events (Grade 3-4)	31			
Hepatic adverse events (Grade 5)	0			
Pulmonary adverse events(Grade 3-4)	6			
Pulmonary adverse events(Grade 5)	0			
Renal adverse events (Grade 3-4)	4			
Renal adverse events (Grade 5)	0			
Skin adverse events (Grade 3-4)	14			
Skin adverse events (Grade 5)	0			
Hypersensitivity adverse event(Grade 3-4)	0			
Hypersensitivity adverse event(Grade 5)	0			
Endocrine adverse events(Grade 3-4)	18			
Endocrine adverse events(Grade 5)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: The Incidence of all high-grade (Grades 3 and higher), select adverse events

End point title	The Incidence of all high-grade (Grades 3 and higher), select adverse events
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End point description:

The number of Participants who reported high-grade (CTCAE v4.0 Grade 3 or higher), select AEs were summarized using the all treated analysis set by system organ class and MedDRA preferred term.

End point type	Secondary
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End point timeframe:

Up to 2 years

End point values	Nivolumab 3mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	1008			
Units: Number				
Gastrointestinal Adverse events (Grade 3-4)	24			
Gastrointestinal adverse events (Grade 5)	0			
Hepatic adverse events (Grade 3-4)	52			
Hepatic adverse events (Grade 5)	1			
Pulmonary adverse events(Grade 3-4)	7			
Pulmonary adverse events(Grade 5)	1			
Renal adverse events (Grade 3-4)	12			
Renal adverse events (Grade 5)	1			
Skin adverse events (Grade 3-4)	20			
Skin adverse events (Grade 5)	0			
Hypersensitivity adverse event(Grade 3-4)	1			
Hypersensitivity adverse event(Grade 5)	0			
Endocrine adverse events(Grade 3-4)	23			
Endocrine adverse events(Grade 5)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to onset (Grades 3-4) of select adverse events

End point title	Median time to onset (Grades 3-4) of select adverse events
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End point description:

Select AEs were summarized according to their incidence as well as their time to onset.

End point type	Secondary
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End point timeframe:

Up to 2 years.

End point values	Nivolumab 3mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	1008			
Units: Weeks				
number (not applicable)				
Endocrine Adverse Event	12			
Gastrointestinal Adverse Event	23.50			
Hepatic Adverse Event	10.14			
Pulmonary Adverse Event	14.86			
Renal Adverse Event	11.71			
Skin Adverse Event	34.36			
Hypersensitivity/infusion reaction	29.57			

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to resolution (Grades 3-4) of select adverse events

End point title	Median time to resolution (Grades 3-4) of select adverse events
End point description:	Select AEs were summarized according to their incidence as well as their time to resolution
End point type	Secondary
End point timeframe:	Up to 2 years

End point values	Nivolumab 3mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	1008			
Units: Weeks				
number (not applicable)				
Endocrine Adverse Event	2.43			
Gastrointestinal Adverse Event	3.71			
Hepatic Adverse Event	9.43			
Pulmonary Adverse Event	2.57			
Renal Adverse Event	1.93			
Skin Adverse Event	5.07			
Hypersensitivity/Infusion Adverse Event	0.29			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

The time from first dosing date to the date of death.

End point type	Secondary
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End point timeframe:

Up to 2 years

End point values	Nivolumab 3mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	1008			
Units: Months				
median (confidence interval 95%)				
Overall survival	21.2 (18.2 to 24.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between first dose and 100 days after last dose (up to 2 years)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	NIVOLUMAB 3 MG/KG IV
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Reporting group description:

Nivolumab 3 mg/kg as a 60-minute IV infusion every 2 weeks.

Serious adverse events	NIVOLUMAB 3 MG/KG IV		
Total subjects affected by serious adverse events			
subjects affected / exposed	593 / 1008 (58.83%)		
number of deaths (all causes)	527		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal neoplasm			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Bowen's disease				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cancer pain				
subjects affected / exposed	5 / 1008 (0.50%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Chronic lymphocytic leukaemia				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infected neoplasm				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial tumour haemorrhage				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Malignant ascites				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm of spinal cord				

subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	278 / 1008 (27.58%)			
occurrences causally related to treatment / all	0 / 310			
deaths causally related to treatment / all	0 / 239			
Melanoma recurrent				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to abdominal cavity				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to adrenals				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metastases to bladder				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to bone				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	16 / 1008 (1.59%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 1			
Metastases to liver				

subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Metastases to lung			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Metastases to skin			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastasis			
subjects affected / exposed	5 / 1008 (0.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			
subjects affected / exposed	15 / 1008 (1.49%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 1		
Neoplasm			

subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pituitary tumour benign				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsil cancer				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tumour associated fever				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tumour flare				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Tumour haemorrhage				

subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Tumour necrosis			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral venous disease			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular occlusion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocele			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 1008 (0.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	7 / 1008 (0.69%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		

General physical health deterioration				
subjects affected / exposed	22 / 1008 (2.18%)			
occurrences causally related to treatment / all	0 / 25			
deaths causally related to treatment / all	0 / 5			
Generalised oedema				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Nodule				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	4 / 1008 (0.40%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	9 / 1008 (0.89%)			
occurrences causally related to treatment / all	2 / 9			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 3			
Treatment failure				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune disorder			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Contrast media allergy			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Penile oedema			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Testicular oedema			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Aspiration			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Atelectasis			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		

Haemoptysis				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	9 / 1008 (0.89%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
subjects affected / exposed	10 / 1008 (0.99%)			
occurrences causally related to treatment / all	10 / 10			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	14 / 1008 (1.39%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 3			
Pulmonary toxicity				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory muscle weakness			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Personality change			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical condition abnormal				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatic enzymes increased				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Csf test abnormal				

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin t increased			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dose calculation error			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fractured sacrum			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	5 / 1008 (0.50%)		
occurrences causally related to treatment / all	4 / 20		
deaths causally related to treatment / all	0 / 0		
Procedural headache			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation necrosis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery occlusion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myocarditis			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery insufficiency			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-Respiratory arrest			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aphasia			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Brachial plexopathy			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Brain stem haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Central nervous system lesion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haematoma			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			
subjects affected / exposed	7 / 1008 (0.69%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Headache			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive encephalopathy			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Narcolepsy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Peripheral nerve lesion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			

subjects affected / exposed	6 / 1008 (0.60%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Sensorimotor disorder			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Status epilepticus			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Miller fisher syndrome			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 1008 (0.99%)		
occurrences causally related to treatment / all	1 / 12		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ectropion			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Iridocyclitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Iritis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Macular hole			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcerative keratitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain				
subjects affected / exposed	13 / 1008 (1.29%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	5 / 1008 (0.50%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Autoimmune pancreatitis				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	7 / 1008 (0.69%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	14 / 1008 (1.39%)			
occurrences causally related to treatment / all	12 / 16			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ileal perforation			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal fistula			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Intussusception			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	10 / 1008 (0.99%)		
occurrences causally related to treatment / all	3 / 12		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	1 / 1		
Cholecystitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatic function abnormal			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic pain			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatomegaly			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertransaminasaemia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-Mediated hepatitis			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis exfoliative			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug eruption			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised erythema			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pemphigoid			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pruritus generalised			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash macular			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 1008 (0.89%)		
occurrences causally related to treatment / all	3 / 9		
deaths causally related to treatment / all	0 / 0		
Autoimmune nephritis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nephrolithiasis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postrenal failure			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 3		
Renal impairment			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Ureteric stenosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adrenal insufficiency			
subjects affected / exposed	5 / 1008 (0.50%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Autoimmune thyroiditis			

subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypophysitis				
subjects affected / exposed	4 / 1008 (0.40%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Hypopituitarism				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hypothyroidism				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Lymphocytic hypophysitis				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Secondary adrenocortical insufficiency				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Steroid withdrawal syndrome				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adrenal haemorrhage				

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mobility decreased			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteochondrosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendonitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal infection			

subjects affected / exposed	4 / 1008 (0.40%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendiceal abscess				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis allergic				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	6 / 1008 (0.60%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	3 / 1008 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	7 / 1008 (0.69%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			

subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	4 / 1008 (0.40%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected dermal cyst				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected lymphocele				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	5 / 1008 (0.50%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Latent tuberculosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	9 / 1008 (0.89%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perirectal abscess			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal sepsis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	13 / 1008 (1.29%)		
occurrences causally related to treatment / all	1 / 14		
deaths causally related to treatment / all	0 / 2		
Pneumonia legionella			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomembranous colitis			

subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	5 / 1008 (0.50%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	8 / 1008 (0.79%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Septic encephalopathy			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	11 / 1008 (1.09%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	4 / 1008 (0.40%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral diarrhoea			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			

subjects affected / exposed	2 / 1008 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tuberculosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			

subjects affected / exposed	4 / 1008 (0.40%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	3 / 1008 (0.30%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	7 / 1008 (0.69%)			
occurrences causally related to treatment / all	4 / 8			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	1 / 1008 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	2 / 1008 (0.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	5 / 1008 (0.50%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	1 / 1			
Hyponatraemia				

subjects affected / exposed	6 / 1008 (0.60%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Hypoproteinaemia			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ketoacidosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 1008 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	NIVOLUMAB 3 MG/KG IV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	857 / 1008 (85.02%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	83 / 1008 (8.23%)		
occurrences (all)	115		
Aspartate aminotransferase			

increased			
subjects affected / exposed	78 / 1008 (7.74%)		
occurrences (all)	90		
Blood alkaline phosphatase increased			
subjects affected / exposed	52 / 1008 (5.16%)		
occurrences (all)	56		
Lipase increased			
subjects affected / exposed	79 / 1008 (7.84%)		
occurrences (all)	155		
Weight decreased			
subjects affected / exposed	63 / 1008 (6.25%)		
occurrences (all)	66		
Nervous system disorders			
Headache			
subjects affected / exposed	122 / 1008 (12.10%)		
occurrences (all)	160		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	126 / 1008 (12.50%)		
occurrences (all)	157		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	168 / 1008 (16.67%)		
occurrences (all)	222		
Fatigue			
subjects affected / exposed	295 / 1008 (29.27%)		
occurrences (all)	355		
Oedema peripheral			
subjects affected / exposed	81 / 1008 (8.04%)		
occurrences (all)	94		
Pyrexia			
subjects affected / exposed	130 / 1008 (12.90%)		
occurrences (all)	182		
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	58 / 1008 (5.75%) 81		
Abdominal pain subjects affected / exposed occurrences (all)	102 / 1008 (10.12%) 113		
Diarrhoea subjects affected / exposed occurrences (all)	210 / 1008 (20.83%) 320		
Constipation subjects affected / exposed occurrences (all)	132 / 1008 (13.10%) 164		
Vomiting subjects affected / exposed occurrences (all)	120 / 1008 (11.90%) 169		
Nausea subjects affected / exposed occurrences (all)	212 / 1008 (21.03%) 299		
Dry mouth subjects affected / exposed occurrences (all)	51 / 1008 (5.06%) 58		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	134 / 1008 (13.29%) 160		
Dyspnoea subjects affected / exposed occurrences (all)	81 / 1008 (8.04%) 94		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	115 / 1008 (11.41%) 135		
Dry skin			

subjects affected / exposed	54 / 1008 (5.36%)		
occurrences (all)	55		
Rash			
subjects affected / exposed	54 / 1008 (5.36%)		
occurrences (all)	72		
Pruritus generalised			
subjects affected / exposed	89 / 1008 (8.83%)		
occurrences (all)	107		
Vitiligo			
subjects affected / exposed	77 / 1008 (7.64%)		
occurrences (all)	81		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	55 / 1008 (5.46%)		
occurrences (all)	56		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	114 / 1008 (11.31%)		
occurrences (all)	125		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	148 / 1008 (14.68%)		
occurrences (all)	199		
Back pain			
subjects affected / exposed	116 / 1008 (11.51%)		
occurrences (all)	140		
Musculoskeletal pain			
subjects affected / exposed	55 / 1008 (5.46%)		
occurrences (all)	60		
Myalgia			
subjects affected / exposed	62 / 1008 (6.15%)		
occurrences (all)	80		
Pain in extremity			
subjects affected / exposed	93 / 1008 (9.23%)		
occurrences (all)	108		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	88 / 1008 (8.73%) 126 54 / 1008 (5.36%) 68		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	143 / 1008 (14.19%) 162		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2015	<p>The inclusion criteria have been expanded and the exclusion criteria have been minimized.</p> <p>The study rationale also offers greater support for the expanded subject population.</p> <p>Treatment-naïve patients have been added.</p> <p>The options for palliative local therapy have also been expanded to meet the needs of the current patient populations.</p> <p>The EORTC QLQ-C30 has been eliminated from the patients' follow up.</p> <p>The time points and frequency of assessments have been updated.</p> <p>The subjects in Cohort 2 will now be analyzed at the same frequency to Cohort 1, so the separate Time and Events Schedule for Cohort 2 was removed.</p> <p>The statistical section has been reformatted to aid understanding of the analyses to support the respective primary, secondary, and exploratory objectives.</p> <p>The timing and frequency of all assessments have been removed from sections of the protocol outside of the Time and Events tables. The endpoints are more representative of the data that will be collected in support of the objectives.</p> <p>The requirement for electrocardiograms has been removed.</p>
19 March 2015	<p>This Amendment removes the inclusion of the treatment-naïve patients, also referred to as the first-line cohort.</p>
02 June 2015	<p>Decreases sample size</p>
28 October 2015	<p>To provide further clarity on the requirements for lipase testing.</p> <p>To provide clarity on dose calculations.</p> <p>To allow the EQ-5D-3L to be completed without an office visit if one is not otherwise needed.</p> <p>The of expectations when lipase results are not available prior to dosing</p> <p>Aligning the footnotes of Table 5.1-2 and Section 5.3, Safety Assessments with the requirements for lipase described in Table 5.1-2.</p> <p>Assessments allowed to be done according to standard of care</p> <p>At what cycle assessments should start and assessment windows</p> <p>When RECIST 1.1 criteria must be used.</p> <p>NOTE: Administrative Letter 04 was not finalized because it was considered to not be needed. However, Administrative Letter 05 was created and finalized with the mistaken understanding that Administrative Letter 04 was finalized.</p>
08 December 2015	<p>Adds dosing windows to the time and events schedule.</p>
17 November 2017	<p>Changed the duration of follow-up from 5 years to 2 years after the first dose of study drug treatment due to a decision to close the study in 2018.</p> <p>This decision was based on adequate safety data obtained since the study's opening in 2014, which are consistent with the known safety profiles of the study drugs. Changed MM Address.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported