Clinical trial results:
A multi-center phase III randomized, double-blind placebo-controlled study of the cancer vaccine Stimuvax® (L-BLP25 or BLP25 liposome vaccine) in non-small cell lung cancer (NSCLC) subjects with unresectable stage III disease.

Summary

EudraCT number	2006-000579-14
Trial protocol	AT BE GB HU CZ SE DE ES DK FR GR IT NL SK IE PT
Global end of trial date	09 September 2015

Results information

Result version number	v1 (current)
This version publication date	19 August 2016
First version publication date	19 August 2016

Trial information

Trial identification

Sponsor protocol code	EMR 63325-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00409188
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Serono, a division of Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Merck KGaA Communication Center, Merck Serono, a division of Merck KGaA, service@merckgroup.com
Scientific contact	Responsible, Merck Serono, a division of Merck KGaA, service@merckgroup.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	08 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2012
Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether the cancer vaccine tecemotide (L-BLP25) in addition to best supportive care is effective in prolonging the lives of subjects with unresectable stage III non-small cell lung cancer, compared to best supportive care alone.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	66 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 65
Country: Number of subjects enrolled	Germany: 109
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 25
Country: Number of subjects enrolled	Poland: 165
Country: Number of subjects enrolled	Romania: 46
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Sweden: 64

Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	United Kingdom: 57
Country: Number of subjects enrolled	United States: 188
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Slovakia: 17
Country: Number of subjects enrolled	Argentina: 40
Country: Number of subjects enrolled	Australia: 43
Country: Number of subjects enrolled	Austria: 28
Country: Number of subjects enrolled	Belgium: 59
Country: Number of subjects enrolled	Brazil: 42
Country: Number of subjects enrolled	Canada: 142
Country: Number of subjects enrolled	China: 1
Country: Number of subjects enrolled	Czech Republic: 95
Worldwide total number of subjects	1513
EEA total number of subjects	919

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)	970
From 65 to 84 years	542
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): 25 January 2007/31 October 2011. Data cut-off for primary endpoint analysis: 08 August 2012. Subjects randomized at 264 centers in 33 countries worldwide.

Pre-assignment

Screening details:

A total of 1908 subjects were screened for eligibility and 1513 subjects were enrolled and randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tecemotide (L-BLP25) + Cyclophosphamide

Arm description:

A single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide was given 3 days before first tecemotide (L-BLP25) vaccination. After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression was documented.

Arm type	Experimental
Investigational medicinal product name	Tecemotide (L-BLP25)
Investigational medicinal product code	
Other name	Stimuvax
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression is documented.

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

Dosage and administration details:

Subjects administered with a single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide 3 days before first tecemotide (L-BLP25) vaccination.

Arm title	Saline + Placebo

Arm description:

A single intravenous infusion of 0.9 percent (%) saline solution in the same calculated dose as cyclophosphamide was given 3 days before first placebo vaccination. After receiving saline, subjects received 8 consecutive weekly subcutaneous vaccinations with placebo at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at Week 13, until disease progression was documented.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received eight consecutive weekly subcutaneous vaccinations with placebo at weeks 0; 1; 2; 3; 4; 5; 6 and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at week 13, until disease progression is documented.

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

Dosage and administration details:

Subjects administered with a single infusion (IV) of 0.9% Saline solution instead of cyclophosphamide but in the same calculated dose given three days before first placebo vaccination.

Number of subjects in period 1	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo
Started	1006	507
Completed	623	332
Not completed	383	175
Ongoing at data cut-off	383	175

Baseline characteristics

Reporting groups	
Reporting group title	Tecemotide (L-BLP25) + Cyclophosphamide

Reporting group description:

A single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide was given 3 days before first tecemotide (L-BLP25) vaccination. After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression was documented.

Reporting group title	Saline + Placebo

Reporting group description:

A single intravenous infusion of 0.9 percent (%) saline solution in the same calculated dose as cyclophosphamide was given 3 days before first placebo vaccination. After receiving saline, subjects received 8 consecutive weekly subcutaneous vaccinations with placebo at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at Week 13, until disease progression was documented.

Reporting group values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo	Total
Number of subjects	1006	507	1513
Age categorical Units: Subjects			
Adults (18-64 years)	657	313	970
From 65 to 84 years	348	194	542
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	60.7	60.9	
standard deviation	± 9.1	± 9	-
Gender, Male/Female Units: subjects			
Female	315	162	477
Male	691	345	1036

End points

End points reporting groups

Reporting group title	Tecemotide (L-BLP25) + Cyclophosphamide

Reporting group description:

A single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide was given 3 days before first tecemotide (L-BLP25) vaccination. After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression was documented.

Reporting group title	Saline + Placebo

Reporting group description:

A single intravenous infusion of 0.9 percent (%) saline solution in the same calculated dose as cyclophosphamide was given 3 days before first placebo vaccination. After receiving saline, subjects received 8 consecutive weekly subcutaneous vaccinations with placebo at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at Week 13, until disease progression was documented.

Subject analysis set title	Tecemotide (L-BLP25) + Cyclophosphamide
Subject analysis set type	Safety analysis

Subject analysis set description:

A single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide was given 3 days before first tecemotide (L-BLP25) vaccination. After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression was documented. Safety analysis set included all subjects who received at least 1 dose of trial treatment (cyclophosphamide, tecemotide, saline, or placebo). Subjects were reported based on the actual treatment received (as-treated).

Subject analysis set title	Saline + Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

A single intravenous infusion of 0.9 percent (%) saline solution in the same calculated dose as cyclophosphamide was given 3 days before first placebo vaccination. After receiving saline, subjects received 8 consecutive weekly subcutaneous vaccinations with placebo at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at Week 13, until disease progression was documented. Safety analysis set included all subjects who received at least 1 dose of trial treatment (cyclophosphamide, tecemotide, saline, or placebo). subjects were reported based on the actual treatment received (as-treated).

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival time was defined as the time from randomization to death. Subjects without events were censored at the last date they were known to be alive or the clinical cut-off date, whatever was earlier. Primary analysis set (modified intention-to-treat [ITT] population) was based on the ITT population but prospectively excluded all subjects (274 subjects) that were randomized during the 6 months (22 Sep 2009 to 22 Mar 2010) prior to the effective date of clinical hold.

End point type	Primary

End point timeframe:

Up to 66 months

End point values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	829	410		
Units: months				
median (confidence interval 95%)	25.6 (22.5 to 29.2)	22.3 (19.6 to 25.5)		

Statistical analyses

Statistical analysis title	Overall Survival Statistical Analysis
Comparison groups	Tecemotide (L-BLP25) + Cyclophosphamide v Saline + Placebo
Number of subjects included in analysis	1239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1566
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.893
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	1.044

Secondary: Time To Symptom Progression (TTSP) as Measured by the Lung Cancer Symptom Scale (LCSS)

End point title	Time To Symptom Progression (TTSP) as Measured by the Lung Cancer Symptom Scale (LCSS)

End point description:

Time to symptom progression (TTSP) was measured by LCSS. Symptomatic progression was defined as an increase (worsening) of the Average Symptomatic Burden Index (ASBI that is, the mean of the six major lung cancer specific symptom scores of the LCSS patient scale – ranging from 0 to 100 where higher score indicates worst outcome). Worsening was defined as a 10% increase in the scale breadth from the baseline score. TTSP is defined as the time from randomization to worsening in ASBI. Subjects without event are censored at the date of the last LCSS assessment. Primary analysis set (modified ITT population) was based on the ITT population but prospectively excluded all subjects (274 subjects) that were randomized during the 6 months (22-Sep-2009 to 22-Mar-2010) prior to the effective date of clinical hold. Number of subjects analysed were the subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Up to 66 months

End point values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	829	409		
Units: months				
median (confidence interval 95%)	14.2 (12.9 to 15.7)	11.4 (9.3 to 13.1)		

Statistical analyses

Statistical analysis title	TTSP Statistical Analysis
Comparison groups	Tecemotide (L-BLP25) + Cyclophosphamide v Saline + Placebo
Number of subjects included in analysis	1238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0226
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.845
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	0.977

Secondary: Time To Progression (TTP)

End point title	Time To Progression (TTP)

End point description:

Time from randomization to disease progression. Disease progression was defined based on Response Evaluation Criteria in Solid Tumors Version 1.0 [RECIST v1.0]) as at least a 20% increase in the sum of the longest diameter of target lesions from nadir, or the appearance of one or more new lesions. Primary analysis set (modified ITT population) was based on the ITT population but prospectively excluded all subjects (274 subjects) that were randomized during the 6 months (22 Sep 2009 to 22 Mar 2010) prior to the effective date of clinical hold.

End point type	Secondary

End point timeframe:

Up to 66 months

End point values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	829	410		
Units: months				

median (confidence interval 95%)	10 (9.1 to 11.5)	8.4 (7.2 to 10.8)		

Statistical analyses

Statistical analysis title	TTP Statistical Analysis
Comparison groups	Tecemotide (L-BLP25) + Cyclophosphamide v Saline + Placebo
Number of subjects included in analysis	1239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0528
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.752
upper limit	1.002

Secondary: One, two- and three-year survival rate

End point title	One, two- and three-year survival rate

End point description:

The percentages of subjects who were alive at 1, 2, and 3 years were calculated as a cumulative percentage by Kaplan-Meier survival analysis approach. Primary analysis set (modified ITT population) was based on the ITT population but prospectively excluded all subjects (274 subjects) that were randomized during the 6 months (22 Sep 2009 to 22 Mar 2010) prior to the effective date of clinical hold.

End point type	Secondary

End point timeframe:

Years 1, 2, and 3

End point values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	829	410		
Units: percentage of subjects				
number (not applicable)				
Year 1	77	74.7		
Year 2	50.8	45.9		
Year 3	40.2	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events and Injection Site Reactions

End point title	Number of Subjects With Treatment Emergent Adverse Events and Injection Site Reactions

End point description:

Treatment -emergent adverse events were defined as those with onset or worsening occurring at or after the first dosing day of study medication and up to 42 days after the last administration of any study drug or the clinical cut-off date. Injection site reactions were reported as assessed by the Investigator. Safety analysis set included all subjects who received at least 1 dose of trial treatment (cyclophosphamide, tecemotide, saline, or placebo). subjects were reported based on the actual treatment received (as-treated).

End point type	Secondary

End point timeframe:

From first dose up to 42 days after the last dose of the trial treatment

End point values	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1024	477		
Units: subjects				
Treatment Emergent Adverse events	938	432		
Injection site reaction	176	56		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 66 months

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least 1 dose of trial treatment (cyclophosphamide, tecemotide, saline, or placebo). Subjects were reported based on the actual treatment received (as-treated).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Tecemotide (L-BLP25) + Cyclophosphamide

Reporting group description:

A single intravenous infusion of 300 milligram per square meter (mg/m^2) (to a maximum 600 mg) of cyclophosphamide was given 3 days before first tecemotide (L-BLP25) vaccination. After receiving cyclophosphamide, subjects received 8 consecutive weekly subcutaneous vaccinations with 806 microgram (mcg) of tecemotide (L-BLP25) at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance vaccinations with 806 mcg of tecemotide (L-BLP25) at 6-week intervals, commencing at Week 13, until disease progression was documented.

Reporting group title	Saline + Placebo

Reporting group description:

A single intravenous infusion of 0.9 percent (%) saline solution in the same calculated dose as cyclophosphamide was given 3 days before first placebo vaccination. After receiving saline, subjects received 8 consecutive weekly subcutaneous vaccinations with placebo at Weeks 0, 1, 2, 3, 4, 5, 6, and 7 followed by maintenance placebo vaccinations at 6-week intervals, commencing at Week 13, until disease progression was documented.

Serious adverse events	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	303 / 1024 (29.59%)	151 / 477 (31.66%)	
number of deaths (all causes)	46	35	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bile duct cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	2 / 1024 (0.20%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 1024 (0.10%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			

subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	32 / 1024 (3.13%)	9 / 477 (1.89%)	
occurrences causally related to treatment / all	0 / 32	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to large intestine			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to kidney			
subjects affected / exposed	2 / 1024 (0.20%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to salivary gland			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to pancreas			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to small intestine			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour invasion			

subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	5 / 1024 (0.49%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral arterial stenosis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporal arteritis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pericardial drainage			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 1024 (0.20%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	2 / 2	0 / 0	
Death			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	9 / 1024 (0.88%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	6 / 1024 (0.59%)	11 / 477 (2.31%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 1024 (0.29%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 1024 (0.20%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
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	4 / 1024 (0.39%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 1024 (0.78%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spermatocele			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial haemorrhage			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	3 / 1024 (0.29%)	7 / 477 (1.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	3 / 1024 (0.29%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	29 / 1024 (2.83%)	13 / 477 (2.73%)	
occurrences causally related to treatment / all	0 / 29	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	11 / 1024 (1.07%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 11	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cyst			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 1024 (0.10%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	13 / 1024 (1.27%)	12 / 477 (2.52%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 1024 (0.20%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	6 / 1024 (0.59%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 1024 (0.98%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	8 / 1024 (0.78%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 1024 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	3 / 1024 (0.29%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
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 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			

subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation associated pain			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation myelopathy			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	7 / 1024 (0.68%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic lung injury			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 1024 (0.10%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 1024 (0.29%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 1024 (0.29%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 1024 (0.78%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	2 / 1024 (0.20%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio−respiratory arrest			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 1024 (0.29%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	3 / 1024 (0.29%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery dissection			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataplexy			

subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	4 / 1024 (0.39%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 1024 (0.20%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	4 / 1024 (0.39%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain−Barre syndrome			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	3 / 1024 (0.29%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	4 / 1024 (0.39%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			

subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 1024 (0.39%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
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			
Haemolytic anaemia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	3 / 1024 (0.29%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocoagulable state			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 1024 (0.29%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 1024 (0.29%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vascular thrombosis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain lower			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphagia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	4 / 1024 (0.39%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal dilatation			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 1024 (0.10%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypothyroidism			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 1024 (0.10%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle atrophy			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	2 / 1024 (0.20%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	4 / 1024 (0.39%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
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 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	9 / 1024 (0.88%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 1024 (0.39%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia primary atypical			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (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	30 / 1024 (2.93%)	14 / 477 (2.94%)	
occurrences causally related to treatment / all	0 / 30	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	7 / 1024 (0.68%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 1024 (0.10%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 1024 (0.20%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1024 (0.10%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 1024 (0.39%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 1024 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 1024 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tecemotide (L-BLP25) + Cyclophosphamide	Saline + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	918 / 1024 (89.65%)	417 / 477 (87.42%)	
Injury, poisoning and procedural complications			
Radiation pneumonitis			
subjects affected / exposed	77 / 1024 (7.52%)	30 / 477 (6.29%)	
occurrences (all)	77	30	
Nervous system disorders			
Dizziness			
subjects affected / exposed	87 / 1024 (8.50%)	37 / 477 (7.76%)	
occurrences (all)	87	37	
Headache			
subjects affected / exposed	123 / 1024 (12.01%)	54 / 477 (11.32%)	
occurrences (all)	123	54	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	195 / 1024 (19.04%)	102 / 477 (21.38%)	
occurrences (all)	195	102	
Asthenia			
subjects affected / exposed	71 / 1024 (6.93%)	29 / 477 (6.08%)	
occurrences (all)	71	29	
Chest pain			

subjects affected / exposed	130 / 1024 (12.70%)	43 / 477 (9.01%)	
occurrences (all)	130	43	
Influenza like illness			
subjects affected / exposed	45 / 1024 (4.39%)	27 / 477 (5.66%)	
occurrences (all)	45	27	
Pyrexia			
subjects affected / exposed	80 / 1024 (7.81%)	41 / 477 (8.60%)	
occurrences (all)	80	41	
Non−cardiac chest pain			
subjects affected / exposed	57 / 1024 (5.57%)	24 / 477 (5.03%)	
occurrences (all)	57	24	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	75 / 1024 (7.32%)	26 / 477 (5.45%)	
occurrences (all)	75	26	
Diarrhoea			
subjects affected / exposed	85 / 1024 (8.30%)	46 / 477 (9.64%)	
occurrences (all)	85	46	
Nausea			
subjects affected / exposed	140 / 1024 (13.67%)	39 / 477 (8.18%)	
occurrences (all)	140	39	
Vomiting			
subjects affected / exposed	65 / 1024 (6.35%)	26 / 477 (5.45%)	
occurrences (all)	65	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	336 / 1024 (32.81%)	133 / 477 (27.88%)	
occurrences (all)	336	133	
Haemoptysis			
subjects affected / exposed	60 / 1024 (5.86%)	32 / 477 (6.71%)	
occurrences (all)	60	32	
Dyspnoea			
subjects affected / exposed	225 / 1024 (21.97%)	103 / 477 (21.59%)	
occurrences (all)	225	103	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	53 / 1024 (5.18%)	27 / 477 (5.66%)	
occurrences (all)	53	27	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	64 / 1024 (6.25%)	25 / 477 (5.24%)	
occurrences (all)	64	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	108 / 1024 (10.55%)	33 / 477 (6.92%)	
occurrences (all)	108	33	
Back pain			
subjects affected / exposed	146 / 1024 (14.26%)	52 / 477 (10.90%)	
occurrences (all)	146	52	
Musculoskeletal pain			
subjects affected / exposed	92 / 1024 (8.98%)	33 / 477 (6.92%)	
occurrences (all)	93	33	
Musculoskeletal chest pain			
subjects affected / exposed	54 / 1024 (5.27%)	22 / 477 (4.61%)	
occurrences (all)	54	22	
Myalgia			
subjects affected / exposed	73 / 1024 (7.13%)	18 / 477 (3.77%)	
occurrences (all)	73	18	
Pain in extremity			
subjects affected / exposed	69 / 1024 (6.74%)	29 / 477 (6.08%)	
occurrences (all)	69	29	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	128 / 1024 (12.50%)	44 / 477 (9.22%)	
occurrences (all)	128	44	
Bronchitis			
subjects affected / exposed	83 / 1024 (8.11%)	38 / 477 (7.97%)	
occurrences (all)	83	38	
Upper respiratory tract infection			

subjects affected / exposed	96 / 1024 (9.38%)	37 / 477 (7.76%)	
occurrences (all)	96	37	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	109 / 1024 (10.64%)	44 / 477 (9.22%)	
occurrences (all)	109	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2007	The purpose of this protocol amendment was: To insert new safety information on the adjuvant component of L-BLP25, as requested by the US Food and Drug Administration (FDA). To explain that elective hospitalization should not be reported as AE or SAE.
23 April 2010	The purpose of this amendment was: To reflect new safety information on L-BLP25. To adjust the eligibility criteria in order to address the new safety information. To implement new subject discontinuation criteria in order to address the new safety information. To specify new special precautions in order to address the new safety information. To implement new assessments in order to address the new safety information. To instruct investigators on how to proceed with subjects who had received the cyclophosphamide/saline infusion but had not yet received the vaccination due to the clinical hold on the L-BLP25 IND by the FDA in March 2010.
05 October 2010	The purpose of this amendment was: considering the new safety information by specifying imaging requirements upon suspicion of encephalitis or neuro inflammatory disorders. clarifying on safety monitoring measures for thrombocytopenia and L-BLP25 content recalculation (930 µg instead of 1000 µg). Implementing changes to sample size considerations and the definition of the Primary Analysis Set in order to minimize a potential impact on the trial results caused by the clinical hold. Introducing the assessment of MUC1-specific immune response in peripheral blood of a subset of subjects, which was carried out within an ancillary clinical trial protocol in several EU countries.
16 December 2011	The purpose of this amendment was: Correct the description of the nominal dose of L-BLP25 (806 µg instead of 930 µg). Clarify changes to the visit and assessment schedule, including safety follow-up for subjects receiving placebo in case of unblinding of the trial or in case of discontinuation of the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 March 2010	Due to reporting of a suspected unexpected serious adverse reaction (SUSAR) of encephalitis in a phase II trial of L-BLP25 in multiple myeloma patients (EMR 63325-008), a clinical hold of the trial was implemented from 19 March 2010 to 14 June 2010.	14 June 2010

Notes:

Limitations and caveats

None reported