



Clinical trial results:

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF (LMW) HEPARIN/EDOXYBAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Summary

EudraCT number	2014-004708-30
Trial protocol	HU CZ BE IT DE ES AT NL
Global end of trial date	15 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

Trial information

Trial identification

Sponsor protocol code	DU176b-D-U311
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02073682
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 63,266

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Daiichi Sankyo US Contact for Clinical Trial Results, Daiichi Sankyo, Inc., 1 908-992-6400, CTRinfo@DSI.com
Scientific contact	Daiichi Sankyo US Contact for Clinical Trial Results, Daiichi Sankyo, Inc., 1 908-992-6400, CTRinfo@DSI.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	12 October 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the non-inferiority of edoxaban (preceded by a short course of LMWH) compared with dalteparin for the prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in subjects with VTE associated with cancer during a 12-month study period. If non-inferiority is established, LMWH/edoxaban will be compared with dalteparin for superiority.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

The study oversight was managed by a Steering Management Coordinating Committee (SMCC) whose members were country coordinators, as well as non-voting representatives of the Sponsor and Academic Research Organization (ARO). In this study, ITREAS functioned as the ARO.

An Executive Committee to the SMCC had a scientific advisory function and was not involved in operational matters.

Ongoing study oversight and management was the responsibility of a joint supervisory committee. The members of this committee were the chairman and co-chair of the SMCC and designated representatives from the Sponsor, Contract Research Organization (CRO), and ARO.

An independent Clinical Events Committee (CEC) was established to objectively adjudicate and categorize the presenting index diagnosis, VTE outcomes, cardiovascular events, bleeding events, selected hepatic events, and death. Adjudicators were blinded to subject treatment allocation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 118
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Austria: 28
Country: Number of subjects enrolled	Belgium: 41
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	France: 122
Country: Number of subjects enrolled	Germany: 59

Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Italy: 90
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	New Zealand: 25
Country: Number of subjects enrolled	United States: 207
Country: Number of subjects enrolled	Canada: 200
Worldwide total number of subjects	1046
EEA total number of subjects	582

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)	507
From 65 to 84 years	521
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

1050 patients were randomized from 114 sites in Western Europe (31), Central Europe (11), South Europe (36), Australia/New Zealand (13) and North America (23)

Pre-assignment

Screening details:

Of 1050 patients randomized, 1046 took study drug and were included in the modified Intent to Treat (mITT) and Safety Analysis Sets

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban

Arm description:

After 5 days of low molecular weight heparin (LMWH), edoxaban treatment daily

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	DU-176b
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After the 5 day treatment with LMWH, patients receive edoxaban 60 mg once daily (QD) as 2 × 30 mg tablets (or 1 × 30 mg tablet QD for patients requiring dose adjustment) for the remainder of the treatment period.

Investigational medicinal product name	Low molecular weight heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Therapeutic doses of subcutaneous LMWH were administered for at least 5 days; this 5-day period may have included the pre-randomization LMWH (if applicable). The choice of parenteral LMWH was up to the treating physician.

Arm title	Dalteparin
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Arm description:

Dalteparin treatment daily

Arm type	Active comparator
Investigational medicinal product name	Dalteparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dalteparin was administered via subcutaneous injection at a dose of 200 IU/kg (maximum daily dose 18,000 IU) for 30 days, and at a dose of 150 IU/kg from Day 31 to the end of treatment.

Number of subjects in period 1	Edoxaban	Dalteparin
Started	522	524
Completed	200	154
Not completed	322	370
Cancer Cured	10	15
Patient Decision: Inconvenience of Dosing	21	78
Investigator Decision: Palliative Treatment Only	10	7
Investigator Decision: Patient Non-compliance	1	2
Low Creatinine Clearance	1	2
Start of New Chemotherapy Regimen	6	3
Investigator Decision: Benefit/Risk Judgment	32	46
Surgery/Medical Procedure	3	1
Prohibited Concomitant Medication Use	-	1
Consent withdrawn by subject	6	8
Adverse event, non-fatal	79	62
Death	86	100
Cancer Progression	53	33
Platelet Count <50,000/mL	1	2
No Reason Provided	11	9
Protocol Violation	1	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Edoxaban
Reporting group description: After 5 days of low molecular weight heparin (LMWH), edoxaban treatment daily	
Reporting group title	Dalteparin
Reporting group description: Dalteparin treatment daily	

Reporting group values	Edoxaban	Dalteparin	Total
Number of subjects	522	524	1046
Age categorical Units: Subjects			
18-64 years	246	261	507
65-84 years	267	254	521
85 years and over	9	9	18
Age continuous Units: years			
median	66	65	
full range (min-max)	22 to 91	21 to 89	-
Gender categorical Units: Subjects			
Female	245	261	506
Male	277	263	540
Type of Cancer Units: Subjects			
Solid Tumor	465	467	932
Haematological Malignancy	56	55	111
Solid Tumor and Haematological Malignancy	1	2	3

End points

End points reporting groups

Reporting group title	Edoxaban
Reporting group description:	
After 5 days of low molecular weight heparin (LMWH), edoxaban treatment daily	
Reporting group title	Dalteparin
Reporting group description:	
Dalteparin treatment daily	

Primary: Number of Patients With Adjudicated Recurrent Venous Thromboembolism (VTE) or Major Bleeding Event

End point title	Number of Patients With Adjudicated Recurrent Venous Thromboembolism (VTE) or Major Bleeding Event
End point description:	
End point type	Primary
End point timeframe:	
12 months	

End point values	Edoxaban	Dalteparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	524		
Units: Patients	67	71		

Statistical analyses

Statistical analysis title	Non-Inferiority Analysis - VTE or Major Bleed
Comparison groups	Edoxaban v Dalteparin
Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.0056
Method	Cox proportional hazard
Parameter estimate	Cox proportional hazard
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.696
upper limit	1.359

Notes:

[1] - Edoxaban was considered non-inferior to dalteparin if the upper limit of the two-sided 95% confidence interval (CI) for the hazard ratio ([LMW] Edoxaban to Dalteparin) was less than 1.5.

Statistical analysis title	Superiority analysis - VTE or Major Bleed
Statistical analysis description: The HR, two-sided CI and superiority p-value for pairwise comparisons versus Dalteparin are based on the Cox proportional hazard model including treatment and the two stratification factors as covariates: the dichotomized bleeding risk and the dichotomized dose-adjustment factor.	
Comparison groups	Edoxaban v Dalteparin
Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8712
Method	Cox proportional hazard

Secondary: Number of Patients With Adjudicated Major Bleeding Events While on Treatment

End point title	Number of Patients With Adjudicated Major Bleeding Events While on Treatment
End point description: The primary safety endpoint was major bleeding events during the On-Treatment Study Period (defined as on-study drug or up to 3 days after the last dose of study drug).	
End point type	Secondary
End point timeframe: 12 months	

End point values	Edoxaban	Dalteparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	524		
Units: Patients	32	16		

Statistical analyses

Statistical analysis title	Cox regression with counting process approach
Statistical analysis description: The HR, 2-sided CI and p-value are based on the Cox regression model with counting process approach for on-treatment including treatment and the 2 stratification factors as covariates: the dichotomized bleeding risk and the dichotomized dose-adjustment factor.	
Comparison groups	Edoxaban v Dalteparin

Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0254
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.089
upper limit	3.657

Secondary: Number of Patients With Recurrent VTE During the Overall Study Period

End point title	Number of Patients With Recurrent VTE During the Overall Study Period
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Edoxaban	Dalteparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	524		
Units: Patients	41	59		

Statistical analyses

Statistical analysis title	Superiority - VTE Overall Study Period
Statistical analysis description:	
The HR, 2-sided CI, and p-value are based on the Cox proportional hazard model including treatment and the 2 stratification factors as covariates: the dichotomized bleeding risk and the dichotomized dose-adjustment factor.	
Comparison groups	Edoxaban v Dalteparin
Number of subjects included in analysis	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0931
Method	Cox proportional hazard
Parameter estimate	Cox proportional hazard
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.476
upper limit	1.059

Secondary: Number of Patients with Additional Categorical Secondary Endpoints during the Overall Study Period

End point title	Number of Patients with Additional Categorical Secondary Endpoints during the Overall Study Period
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Edoxaban	Dalteparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	524		
Units: Patients				
Recurrent Deep Vein Thrombosis (DVT)	19	35		
Recurrent Non-Fatal Pulmonary Embolism (PE)	21	24		
VTE-Related Death	6	4		
Recurrent VTE, Major Bleed or All-Cause Death	235	228		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Edoxaban
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Reporting group description:

After 5 days of low molecular weight heparin (LMWH), edoxaban treatment daily

Reporting group title	Dalteparin
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Reporting group description:

Dalteparin treatment daily

Serious adverse events	Edoxaban	Dalteparin	
Total subjects affected by serious adverse events			
subjects affected / exposed	276 / 522 (52.87%)	251 / 524 (47.90%)	
number of deaths (all causes)	206	192	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	2 / 522 (0.38%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Adenocarcinoma gastric			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma pancreas			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder cancer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	0 / 522 (0.00%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
Cervix cancer metastatic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon cancer metastatic			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Colorectal cancer			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Colorectal cancer metastatic			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Endometrial cancer			
subjects affected / exposed	2 / 522 (0.38%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Endometrial cancer metastatic			
subjects affected / exposed	1 / 522 (0.19%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Gallbladder cancer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			

subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Huerthle cell carcinoma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liposarcoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lung adenocarcinoma metastatic			
subjects affected / exposed	3 / 522 (0.57%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Lung cancer metastatic			
subjects affected / exposed	3 / 522 (0.57%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 4	
Lung neoplasm malignant			
subjects affected / exposed	8 / 522 (1.53%)	6 / 524 (1.15%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 8	0 / 6	
Malignant neoplasm of unknown primary site			

subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant anorectal neoplasm			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	69 / 522 (13.22%)	67 / 524 (12.79%)	
occurrences causally related to treatment / all	1 / 69	0 / 67	
deaths causally related to treatment / all	0 / 68	0 / 67	
Metastases to central nervous system			
subjects affected / exposed	3 / 522 (0.57%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to lymph nodes			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to rectum			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic carcinoma of the bladder			

subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 522 (0.19%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm malignant			
subjects affected / exposed	1 / 522 (0.19%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Neoplasm progression			
subjects affected / exposed	24 / 522 (4.60%)	21 / 524 (4.01%)	
occurrences causally related to treatment / all	0 / 24	0 / 21	
deaths causally related to treatment / all	0 / 24	0 / 21	
Non-small cell lung cancer			
subjects affected / exposed	2 / 522 (0.38%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			
subjects affected / exposed	0 / 522 (0.00%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Ovarian cancer metastatic			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	4 / 522 (0.77%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	2 / 522 (0.38%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Plasma cell myeloma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 522 (0.00%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Prostate cancer metastatic			
subjects affected / exposed	3 / 522 (0.57%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal cancer metastatic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sarcoma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell carcinoma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
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	13 / 522 (2.49%)	8 / 524 (1.53%)	
occurrences causally related to treatment / all	5 / 13	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 522 (0.19%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintended pregnancy			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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			
Adverse drug reaction			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter site haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 522 (0.77%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Disease progression			
subjects affected / exposed	4 / 522 (0.77%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Euthanasia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			

subjects affected / exposed	2 / 522 (0.38%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Oedema peripheral			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 522 (0.57%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			

subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 522 (0.19%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Asthma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 522 (0.57%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	5 / 522 (0.96%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	4 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 522 (0.19%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	8 / 522 (1.53%)	16 / 524 (3.05%)	
occurrences causally related to treatment / all	3 / 9	3 / 17	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	7 / 522 (1.34%)	6 / 524 (1.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 6	0 / 4	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Creatinine renal clearance decreased subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased subjects affected / exposed	0 / 522 (0.00%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall subjects affected / exposed	0 / 522 (0.00%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haematoma subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract stoma complication subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 522 (0.57%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 522 (0.19%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Cardiac failure			
subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiovascular disorder			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac mass			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 522 (0.19%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulseless electrical activity			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
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	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal ganglia haemorrhage			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 522 (0.57%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 522 (0.38%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhagic stroke			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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	6 / 522 (1.15%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	2 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukoencephalopathy			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
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			
Anaemia			
subjects affected / exposed	4 / 522 (0.77%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 522 (0.00%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal incarcerated hernia subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage subjects affected / exposed	11 / 522 (2.11%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	8 / 12	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 522 (0.00%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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	2 / 522 (0.38%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	4 / 522 (0.77%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	5 / 522 (0.96%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 522 (0.77%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 522 (0.00%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	5 / 522 (0.96%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 522 (0.38%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal infarct			

subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 522 (0.19%)	1 / 524 (0.19%)	
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	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	2 / 522 (0.38%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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	1 / 522 (0.19%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal sepsis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (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	16 / 522 (3.07%)	13 / 524 (2.48%)	
occurrences causally related to treatment / all	0 / 17	0 / 13	
deaths causally related to treatment / all	0 / 4	0 / 6	
Pneumonia bacterial			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative abscess			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 522 (0.00%)	3 / 524 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 522 (0.77%)	7 / 524 (1.34%)	
occurrences causally related to treatment / all	0 / 4	1 / 7	
deaths causally related to treatment / all	0 / 2	0 / 4	
Septic shock			
subjects affected / exposed	3 / 522 (0.57%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Staphylococcal sepsis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 522 (0.19%)	4 / 524 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 524 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	4 / 522 (0.77%)	2 / 524 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Dehydration			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 522 (0.00%)	1 / 524 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Edoxaban	Dalteparin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 522 (14.37%)	67 / 524 (12.79%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	34 / 522 (6.51%)	37 / 524 (7.06%)	
occurrences (all)	40	45	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	41 / 522 (7.85%)	30 / 524 (5.73%)	
occurrences (all)	44	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2015	Addendum A (Protocol V3.0), dated 16 Jun 2015, made the following changes: <ul style="list-style-type: none">- Addendum A incorporated changes based on feedback from the Czech Republic Health Authorities. This country-specific addendum applied to all Czech Republic sites and subjects enrolled into DU176b-D-U311
17 December 2015	Amendment 1 (Protocol V2.0), dated 17 Dec 2015, made the following changes: <ul style="list-style-type: none">- The number of study sites was increased- Frequency of liver function test monitoring was reduced- A hierarchical process for statistical analysis was described- Minor inconsistencies throughout the protocol were corrected in order to add clarity to the text/study procedures- Protocol title was changed
11 January 2016	Amendment 2 (Protocol V3.0), dated 11 Jan 2016, made the following changes: <ul style="list-style-type: none">- The updated protocol title in Version 2.0 was reverted back to original as in Version 1.0 (A Phase 3b, prospective, randomized, open-label, blind evaluator (PROBE) study evaluating the efficacy and safety of LMW heparin/edoxaban versus dalteparin in VTE associated with cancer)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported