

**Clinical trial results:****select-d: Anticoagulation Therapy in SELECTed Cancer Patients at Risk of Recurrence of Venous Thromboembolism****Summary**

EudraCT number	2012-005589-37
Trial protocol	GB
Global end of trial date	31 July 2019

**Results information**

Result version number	v1 (current)
This version publication date	16 August 2020
First version publication date	16 August 2020
Summary attachment (see zip file)	Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D) (JCO.2018.78_AY.pdf) Treatment of cancer-associated venous thromboembolism: 12month outcomes of the placebo versus rivaroxaban randomization of the SELECT-D trial (SELECT-D: 12m) (select-d_12m_jth.pdf) Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis (blood.2020005819.pdf)

**Trial information****Trial identification**

Sponsor protocol code	REGO-2013-076
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**Additional study identifiers**

ISRCTN number	ISRCTN86712308
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	University of Warwick
Sponsor organisation address	Gibbet Hill Campus, Coventry, United Kingdom, CV4 7AL
Public contact	Jaclyn Brown, Warwick Clinical Trials Unit, +44 2476150086, j.brown.10@warwick.ac.uk
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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	No

Notes:

**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	31 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2019
Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

**General information about the trial**

Main objective of the trial:

To assess VTE recurrence in SELECTeD cancer patients at risk of recurrence of VTE treated with rivaroxaban or dalteparin

Protection of trial subjects:

A detailed safety analysis was conducted after the first 220 patients. Confidential reports including recruitment, protocol compliance, safety and outcome data were reviewed by the IDMC throughout the trial.

Background therapy:

In 2013 when select-d started, the standard treatment and prevention of recurrence venous thromboembolism (VTE) in the cancer population (in the Western world) was low molecular weight heparin (LMWH) which is administered by subcutaneous injection. This was based on the CLOT study (Lee et al, 2003) published a decade earlier which showed that the LMWH, dalteparin, was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. Dalteparin was the only LMWH licensed for use in cancer patients at that time.

Evidence for comparator:

The direct oral anticoagulants – the direct thrombin inhibitor, dabigatran and Factor Xa inhibitors, rivaroxaban and apixaban were emerging as 'novel' anticoagulants for treatment of all patients with VTE in 2013. The phase III trials of rivaroxaban vs short-term LMWH followed by warfarin for treatment of VTE, 'EINSTEIN', were large (>4000 patients) and included ~5% of cancer patients. The standard treatment of warfarin was not standard for cancer patients. However, the efficacy and safety of warfarin and rivaroxaban were similar. Head to head trials of rivaroxaban and LMWH were recommended in the pooled 'EINSTEIN' trials (Prins et al, 2013); select-d was thus begun.

Actual start date of recruitment	01 October 2013
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	United Kingdom: 406
Worldwide total number of subjects	406
EEA total number of subjects	406

Notes:

<b>Subjects enrolled per age group</b>	
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)	143
From 65 to 84 years	255
85 years and over	8

## Subject disposition

### Recruitment

Recruitment details:

Patients with active cancer with a primary presentation of VTE were recruited from 61 participating sites, between September 2013 and December 2016.

### Pre-assignment

Screening details:

Screening Logs were maintained to document all patients considered for the trial but subsequently excluded. Where possible, the reason for non-entry to the trial was documented. Patient names, hospital numbers or other personal identifiers were not recorded, only initials.

### Period 1

Period 1 title	First randomisation to 6 months
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Dalteparin

Arm description:

Modes of action

Dalteparin sodium is an antithrombotic agent, which acts mainly through its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT).

Therapeutic indication

- Peri- and post-operative surgical thromboprophylaxis.
- The prophylaxis of proximal deep venous thrombosis in patients bedridden due to a medical condition, including, but not limited to; congestive cardiac failure (NYHA class III or IV), acute respiratory failure or acute infection, who also have a predisposing risk factor for venous thromboembolism such as age over 75 years, obesity, cancer or previous history of VTE.
- Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.

Doses

Month 1: 200 IU/kg total body weight once daily, using fixed dose syringes.

Months 2-6: 150 IU/kg once daily

Arm type	Active comparator
Investigational medicinal product name	Dalteparin
Investigational medicinal product code	Dalteparin
Other name	Fragmin
Pharmaceutical forms	Suspension for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

Doses

Month 1: 200 IU/kg total body weight once daily, using fixed dose syringes.

Months 2-6: 150 IU/kg once daily using fixed dose syringes.

Route of administration

Subcutaneous injection, preferably into the abdominal subcutaneous tissue or into the lateral part of the thigh.

Formulation

- Fragmin 5,000 IU
- Fragmin 7,500 IU/0.3 ml solution for injection
- Fragmin 10,000 IU/0.4 ml solution for injection
- Fragmin 12,500 IU/0.5 ml solution for injection
- Fragmin 15,000 IU/0.6 ml solution for injection
- Fragmin 18,000 IU/0.72 ml solution for injection

<b>Arm title</b>	Rivaroxaban
Arm description:	
Modes of action	
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.	
Therapeutic indication	
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.	
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.	
Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	Rivaroxaban
Other name	Xarelto
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Doses

15mg twice daily for the first three weeks.

20mg once daily for the remainder of the 6 month treatment period.

Route of administration

Oral

Formulation

- Xarelto 15 mg film-coated tablets
- Xarelto 20 mg film-coated tablets

<b>Number of subjects in period 1</b>	Dalteparin	Rivaroxaban
Started	203	203
Completed	203	203

## Period 2

Period 2 title	Second randomisation from 6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Carer, Assessor

Blinding implementation details:

Rivaroxaban and placebo were packaged and delivered by an external company (Sharp Clinical, Wales) to the participating sites with a drug pack number on tablet bottle.

When a patient was recruited to the second randomisation, the randomisation officer supplied the drug pack number, confirmed by email and faxed the notification to the site pharmacy department.

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo
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Arm description:

Placebo after 6 months of initial anticoagulation therapy

Arm type	Placebo
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Investigational medicinal product name	placebo
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Investigational medicinal product code	placebo
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Other name	
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

no dose

oral - one tablet, once a day

<b>Arm title</b>	Rivaroxaban
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Arm description:

Rivaroxaban after initial 6 months of anticoagulation therapy

Arm type	Experimental
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Investigational medicinal product name	Rivaroxaban
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Investigational medicinal product code	Rivaroxaban
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Other name	Xarelto
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

Doses

15mg twice daily for the first three weeks.

20mg once daily for the remainder of the 6 month treatment period.

Route of administration

Oral

Formulation

- Xarelto 15 mg film-coated tablets

- Xarelto 20 mg film-coated tablets

Number of subjects in period 2 <sup>[1]</sup>	Placebo	Rivaroxaban
Started	46	46
Completed	46	46

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Justification. Period 2 was a second randomisation for participants who finished the first - patient status and choice, and clinician preference meant that the numbers for the second randomisation of further anticoagulation versus placebo, were much smaller.

## Baseline characteristics

### Reporting groups

Reporting group title	Dalteparin
Reporting group description:	
Modes of action	
Dalteparin sodium is an antithrombotic agent, which acts mainly through its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT).	
Therapeutic indication	
<ul style="list-style-type: none"> <li>- Peri- and post-operative surgical thromboprophylaxis.</li> <li>- The prophylaxis of proximal deep venous thrombosis in patients bedridden due to a medical condition, including, but not limited to; congestive cardiac failure (NYHA class III or IV), acute respiratory failure or acute infection, who also have a predisposing risk factor for venous thromboembolism such as age over 75 years, obesity, cancer or previous history of VTE.</li> <li>- Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.</li> </ul>	
Doses	
Month 1: 200 IU/kg total body weight once daily, using fixed dose syringes.	
Months 2-6: 150 IU/kg once daily	

Reporting group title	Rivaroxaban
Reporting group description:	
Modes of action	
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.	
Therapeutic indication	
<ul style="list-style-type: none"> <li>- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age <math>\geq</math> 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.</li> <li>- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.</li> </ul>	

Reporting group values	Dalteparin	Rivaroxaban	Total
Number of subjects	203	203	406
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	70	73	143
From 65-84 years	128	127	255
85 years and over	5	3	8
Age continuous			
Units: years			
median	67	67	
full range (min-max)	34 to 87	22 to 87	-

Gender categorical Units: Subjects			
Female	105	87	192
Male	98	116	214
Stage of disease at randomisation Units: Subjects			
Early/locally advanced disease	83	81	164
Metastatic disease	114	118	232
Haematological malignancy	6	4	10
Qualifying VTE Units: Subjects			
Symptomatic VTE	99	96	195
Incidental PE	104	107	211



## End points

### End points reporting groups

Reporting group title	Dalteparin
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Reporting group description:

Modes of action

Dalteparin sodium is an antithrombotic agent, which acts mainly through its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT).

Therapeutic indication

- Peri- and post-operative surgical thromboprophylaxis.
- The prophylaxis of proximal deep venous thrombosis in patients bedridden due to a medical condition, including, but not limited to; congestive cardiac failure (NYHA class III or IV), acute respiratory failure or acute infection, who also have a predisposing risk factor for venous thromboembolism such as age over 75 years, obesity, cancer or previous history of VTE.
- Patients with solid tumours: Extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence.

Doses

Month 1: 200 IU/kg total body weight once daily, using fixed dose syringes.

Months 2-6: 150 IU/kg once daily

Reporting group title	Rivaroxaban
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Reporting group description:

Modes of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Therapeutic indication

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Reporting group title	Placebo
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Reporting group description:

Placebo after 6 months of initial anticoagulation therapy

Reporting group title	Rivaroxaban
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Reporting group description:

Rivaroxaban after initial 6 months of anticoagulation therapy

### Primary: VTE recurrence

End point title	VTE recurrence
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End point description:

End point type	Primary
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End point timeframe:

From randomisation until 6 months

End point values	Dalteparin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: Subjects	18	8		

## Statistical analyses

Statistical analysis title	Time to a VTE recurrence
Statistical analysis description:	
Time to a VTE recurrence was calculated from the date of random assignment to the date of first VTE recurrence event or censored at the analysis date of 6 months or date last known to be VTE recurrence free, if earlier. A cox regression model was used to obtain hazard ratio and associated 95% confidence intervals.	
Comparison groups	Dalteparin v Rivaroxaban
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.99

## Secondary: Major bleeding

End point title	Major bleeding
End point description:	
End point type	Secondary
End point timeframe:	
from randomisation until 6 months	

End point values	Dalteparin	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	203		
Units: Subjects	6	11		

## Statistical analyses

<b>Statistical analysis title</b>	Time to a major bleed
Statistical analysis description:	
Time to a major bleed was calculated from randomisation until date of first major bleed or censored at the analysis date of 6 months or at the date last known to not have a major bleed if earlier. A cox regression model was used to obtain hazard ratio and associated 95% confidence intervals.	
Comparison groups	Dalteparin v Rivaroxaban
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	4.97

## Secondary: VTE recurrences from second randomisation

End point title	VTE recurrences from second randomisation
End point description:	
End point type	Secondary
End point timeframe:	
From second randomisation to 6 months post second randomisation	

<b>End point values</b>	Placebo	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Subjects	6	2		

## Statistical analyses

<b>Statistical analysis title</b>	Time from second randomisation to a VTE recurrence
Statistical analysis description:	
Time from second randomisation to a VTE recurrence was calculated from the date of second random assignment to the date of a VTE recurrence event or censored at the analysis date of 6 months after randomisation or date last known to be VTE recurrence free, if earlier. A cox regression model was used to obtain hazard ratio and associated 95% confidence intervals.	
Comparison groups	Placebo v Rivaroxaban

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.58

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### Secondary: Major bleeding after second randomisation

End point title	Major bleeding after second randomisation
End point description:	
End point type	Secondary
End point timeframe:	
From second randomisation until 6 months post second randomisation	

End point values	Placebo	Rivaroxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Subjects	0	2		

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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All SAEs that occurred between trial entry and 30 days after the end of the trial treatment were reported. Events occurring outside of this time period were reported if the investigator felt that it was medically important.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

### Reporting groups

Reporting group title	Dalteparin
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Reporting group description:

Dalteparin

Reporting group title	Rivaroxaban
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Reporting group description:

Rivaroxaban

Reporting group title	Placebo
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Reporting group description:

Patients allocated to placebo at second randomisation after initial 6 months of anticoagulation

Reporting group title	Rivaroxaban second randomisation
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Reporting group description:

Patients allocated to rivaroxaban at second randomisation after initial 6 months of anticoagulation

Serious adverse events	Dalteparin	Rivaroxaban	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 203 (31.03%)	76 / 203 (37.44%)	8 / 46 (17.39%)
number of deaths (all causes)	56	48	5
number of deaths resulting from adverse events	5	5	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Treatment related secondary malignancy			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Other			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	4 / 203 (1.97%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 203 (0.00%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	4 / 203 (1.97%)	6 / 203 (2.96%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Flu like symptoms			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	4 / 203 (1.97%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Other			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress syndrome			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cough			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	13 / 203 (6.40%)	8 / 203 (3.94%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 16	4 / 10	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 203 (0.00%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			



subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusion			
subjects affected / exposed	2 / 203 (0.99%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine renal clearance increased			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	2 / 203 (0.99%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	4 / 203 (1.97%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Bruising			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 203 (0.00%)	5 / 203 (2.46%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraoperative respiratory injury			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 203 (0.99%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Cardiac disorder			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Heart failure			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oculomotor nerve disorder			

subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Syncope			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 203 (1.48%)	7 / 203 (3.45%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 3	6 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 203 (1.48%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	6 / 203 (2.96%)	7 / 203 (3.45%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	1 / 6	2 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anal haemorrhage			

subjects affected / exposed	0 / 203 (0.00%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal pain			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	3 / 203 (1.48%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	8 / 203 (3.94%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 8	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 203 (0.49%)	3 / 203 (1.48%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dysphagia			
subjects affected / exposed	0 / 203 (0.00%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			

subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal incontinence			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis oral			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	7 / 203 (3.45%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral haemorrhage			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 203 (0.49%)	6 / 203 (2.96%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Vomiting			
subjects affected / exposed	7 / 203 (3.45%)	9 / 203 (4.43%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 7	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
jejunal obstruction			

subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	0 / 203 (0.00%)	2 / 203 (0.99%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 203 (2.46%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 203 (0.00%)	4 / 203 (1.97%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	1 / 203 (0.49%)	2 / 203 (0.99%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			



subjects affected / exposed	0 / 203 (0.00%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	3 / 203 (1.48%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall pain			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised muscle weakness			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			

subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness lower limb			
subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial infection			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Device related infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			

subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	3 / 203 (1.48%)	3 / 203 (1.48%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	12 / 203 (5.91%)	11 / 203 (5.42%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 12	0 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal infection			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 203 (1.48%)	3 / 203 (1.48%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	2 / 203 (0.99%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	3 / 203 (1.48%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic infection			
subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 203 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 203 (0.49%)	1 / 203 (0.49%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	0 / 203 (0.00%)	0 / 203 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Rivaroxaban second randomisation		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 46 (17.39%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Treatment related secondary malignancy			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Flu like symptoms			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Malaise			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress syndrome			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Epistaxis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination			



subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Creatinine renal clearance increased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fracture				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Other				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraoperative respiratory injury				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorder				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heart failure				

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oculomotor nerve disorder			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stroke			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			

subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colonic obstruction				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colonic perforation				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal haemorrhage				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecal incontinence				

subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucositis oral				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
jejunal obstruction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Other			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Portal vein thrombosis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		



Back pain				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest wall pain				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised muscle weakness				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint effusion				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Other				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle weakness lower limb				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Abdominal infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anorectal infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Other				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint infection				

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritoneal infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			

subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Other			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Dalteparin	Rivaroxaban	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 203 (62.56%)	146 / 203 (71.92%)	28 / 46 (60.87%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed <sup>[1]</sup>	27 / 159 (16.98%)	19 / 158 (12.03%)	3 / 40 (7.50%)
occurrences (all)	33	22	3
Creatinine renal clearance increased			
subjects affected / exposed <sup>[2]</sup>	22 / 159 (13.84%)	18 / 158 (11.39%)	8 / 40 (20.00%)
occurrences (all)	28	23	9
Platelet count decreased			
subjects affected / exposed <sup>[3]</sup>	25 / 159 (15.72%)	19 / 158 (12.03%)	2 / 40 (5.00%)
occurrences (all)	31	21	2
Vascular disorders			
Hypotension			
subjects affected / exposed <sup>[4]</sup>	8 / 159 (5.03%)	7 / 158 (4.43%)	1 / 40 (2.50%)
occurrences (all)	8	7	1
Nervous system disorders			
Dizziness			
subjects affected / exposed <sup>[5]</sup>	16 / 159 (10.06%)	29 / 158 (18.35%)	3 / 40 (7.50%)
occurrences (all)	18	32	5
Headache			
subjects affected / exposed <sup>[6]</sup>	13 / 159 (8.18%)	16 / 158 (10.13%)	3 / 40 (7.50%)
occurrences (all)	14	20	4
Peripheral sensory neuropathy			
subjects affected / exposed <sup>[7]</sup>	9 / 159 (5.66%)	9 / 158 (5.70%)	1 / 40 (2.50%)
occurrences (all)	11	10	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed <sup>[8]</sup>	56 / 159 (35.22%)	51 / 158 (32.28%)	7 / 40 (17.50%)
occurrences (all)	73	67	11
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed <sup>[9]</sup> occurrences (all)	87 / 159 (54.72%) 114	89 / 158 (56.33%) 118	13 / 40 (32.50%) 19
Fever subjects affected / exposed <sup>[10]</sup> occurrences (all)	5 / 159 (3.14%) 5	8 / 158 (5.06%) 8	2 / 40 (5.00%) 3
Injection site reaction subjects affected / exposed <sup>[11]</sup> occurrences (all)	29 / 159 (18.24%) 34	2 / 158 (1.27%) 2	1 / 40 (2.50%) 2
Pain subjects affected / exposed occurrences (all)	6 / 203 (2.96%) 6	5 / 203 (2.46%) 6	0 / 46 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed <sup>[12]</sup> occurrences (all)	31 / 159 (19.50%) 36	39 / 158 (24.68%) 45	10 / 40 (25.00%) 12
Constipation subjects affected / exposed <sup>[13]</sup> occurrences (all)	33 / 159 (20.75%) 45	33 / 158 (20.89%) 39	6 / 40 (15.00%) 6
Diarrhoea subjects affected / exposed occurrences (all)	34 / 203 (16.75%) 40	36 / 203 (17.73%) 44	7 / 46 (15.22%) 10
Dyspepsia subjects affected / exposed <sup>[14]</sup> occurrences (all)	30 / 159 (18.87%) 39	21 / 158 (13.29%) 27	6 / 40 (15.00%) 7
Nausea subjects affected / exposed <sup>[15]</sup> occurrences (all)	39 / 159 (24.53%) 46	43 / 158 (27.22%) 50	7 / 40 (17.50%) 11
Vomiting subjects affected / exposed <sup>[16]</sup> occurrences (all)	24 / 159 (15.09%) 26	23 / 158 (14.56%) 24	5 / 40 (12.50%) 5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed <sup>[17]</sup> occurrences (all)	11 / 159 (6.92%) 13	8 / 158 (5.06%) 10	4 / 40 (10.00%) 4
Epistaxis			

subjects affected / exposed occurrences (all)	5 / 203 (2.46%) 7	10 / 203 (4.93%) 12	0 / 46 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed <sup>[18]</sup> occurrences (all)	19 / 159 (11.95%) 22	16 / 158 (10.13%) 17	3 / 40 (7.50%) 5
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	3 / 203 (1.48%) 3	10 / 203 (4.93%) 13	1 / 46 (2.17%) 1
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed <sup>[19]</sup> occurrences (all)	28 / 159 (17.61%) 32	36 / 158 (22.78%) 44	10 / 40 (25.00%) 13

<b>Non-serious adverse events</b>	Rivaroxaban second randomisation		
Total subjects affected by non-serious adverse events subjects affected / exposed	29 / 46 (63.04%)		
Investigations Alanine aminotransferase increased subjects affected / exposed <sup>[1]</sup> occurrences (all)  Creatinine renal clearance increased subjects affected / exposed <sup>[2]</sup> occurrences (all)  Platelet count decreased subjects affected / exposed <sup>[3]</sup> occurrences (all)	2 / 39 (5.13%) 2  5 / 39 (12.82%) 8  5 / 39 (12.82%) 6		
Vascular disorders Hypotension subjects affected / exposed <sup>[4]</sup> occurrences (all)	2 / 39 (5.13%) 2		
Nervous system disorders Dizziness subjects affected / exposed <sup>[5]</sup> occurrences (all)  Headache	6 / 39 (15.38%) 7		

subjects affected / exposed <sup>[6]</sup> occurrences (all)	2 / 39 (5.13%) 2		
Peripheral sensory neuropathy subjects affected / exposed <sup>[7]</sup> occurrences (all)	0 / 39 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed <sup>[8]</sup> occurrences (all)	11 / 39 (28.21%) 17		
General disorders and administration site conditions Fatigue subjects affected / exposed <sup>[9]</sup> occurrences (all)	17 / 39 (43.59%) 23		
Fever subjects affected / exposed <sup>[10]</sup> occurrences (all)	3 / 39 (7.69%) 4		
Injection site reaction subjects affected / exposed <sup>[11]</sup> occurrences (all)	0 / 39 (0.00%) 0		
Pain subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed <sup>[12]</sup> occurrences (all)	5 / 39 (12.82%) 6		
Constipation subjects affected / exposed <sup>[13]</sup> occurrences (all)	4 / 39 (10.26%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 46 (10.87%) 5		
Dyspepsia subjects affected / exposed <sup>[14]</sup> occurrences (all)	3 / 39 (7.69%) 3		
Nausea			



subjects affected / exposed <sup>[15]</sup>	5 / 39 (12.82%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed <sup>[16]</sup>	3 / 39 (7.69%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed <sup>[17]</sup>	1 / 39 (2.56%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed <sup>[18]</sup>	0 / 39 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed <sup>[19]</sup>	6 / 39 (15.38%)		
occurrences (all)	8		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.



exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The numbers exposed was different because the total of those exposed was the number of patients that research team had a trial investigation form and therefore had information on non-serious AEs. The patients without trial investigation forms, the research team did not know whether they suffered any non-serious AEs or not.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2016	<p>Amended protocol to reflect new reduced sample size of 400 and included statistical justification.</p> <p>Updated wording on secondary end points 'VTE recurrence rates for 12 months and 6 months treatment' and 'VTE recurrence rates for RVT and no RVT' was removed, as these were considered analyses of the primary endpoint for different subgroups rather than secondary endpoints.</p> <p>Updated primary outcome measure wording to VTE recurrence (including symptomatic VTE and incidental PE).</p> <p>Updated exclusion criteria.Changes included:</p> <ul style="list-style-type: none"><li>- Addition of the exclusion criterion 'Patients with primary oesophageal or gastro-oesophageal cancer'. Please see Notification of Substantial Amendment Form for justification.</li><li>- Clarification that patients are excluded if they are taking any treatment dose of anticoagulants.</li><li>- Addition of 'dual antiplatelet therapy' exclusion criterion</li><li>- Extension of the time window between starting anticoagulant for the episode of VTE and the planned randomised treatment start time, to 96 hours where necessary</li><li>- Addition of 'Patients with a previous history of VTE' as an exclusion criterion</li><li>- Addition of 'Body weight &lt; 40kg at time of venous thromboembolic event' as an exclusion criterion</li></ul> <p>Updated inclusion criteria. Changes included:</p> <ul style="list-style-type: none"><li>- Clarification that DVT must be a lower extremity proximal DVT</li><li>- An update to the units used for haemoglobin (Hb)</li><li>- Minor change in creatinine clearance value (changed from &gt; 30 ml per minute to ≥ 30ml per minute)</li></ul> <p>Updated inclusion of sub study. The aim of this sub study is to provide qualitative data on the experiences of patients receiving an anticoagulant as part of the select-d trial and their family carers, to complement the safety and efficacy data derived from the main trial.</p> <p>Added ISRCTN number.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was a pilot study and therefore not powered to test the differences.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29746227>

<http://www.ncbi.nlm.nih.gov/pubmed/31995662>

<http://www.ncbi.nlm.nih.gov/pubmed/32396939>