



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 |
|-----------------------|---------------|

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 |
|------------------|------------|

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

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|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

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

| 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