



Clinical trial results:

Evaluation of the Safety and Efficacy of an Edoxaban-based Compared to a Vitamin K Antagonist-based Antithrombotic Regimen in Subjects with Atrial Fibrillation Following Successful Percutaneous Coronary Intervention (PCI) With Stent Placement (ENTRUST AF-PCI)

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2016-002683-14 |
| Trial protocol | FR IE GB NL DE LT ES AT HU PT BE IT |
| Global end of trial date | 06 June 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 27 May 2020 |
| First version publication date | 27 May 2020 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | DSE-EDO-01-15-EU |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02866175 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Daiichi Sankyo Europe, GmbH, a Daiichi Sankyo Company |
| Sponsor organisation address | Zielstattstrasse 48, Munich, Germany, 81379 |
| Public contact | Late Phase Clinical Operations, Daiichi Sankyo Europe GmbH, +49 89 7808 614, Petra.laeis@daiichi-sankyo.eu |
| Scientific contact | Late Phase Clinical Operations, Daiichi Sankyo Europe GmbH, +49 89 7808 614, Petra.laeis@daiichi-sankyo.eu |

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 | 07 January 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y₁₂ antagonist against a regimen of a vitamin K antagonist (VKA) in combination with clopidogrel or another P2Y₁₂ antagonist and at least 1 month acetylsalicylic acid (ASA) in subjects with atrial fibrillation (AF) following successful PCI with stent placement in terms of the incidence of major or clinically relevant non-major International Society on Thrombosis and Hemostasis (ISTH)-defined bleeding (MCRB).

Protection of trial subjects:

The study protocol, amendments, informed consent forms, and information sheets were approved by the appropriate and applicable Independent Ethics Committees or Institutional Review Boards. The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6(R2) for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995) and applicable regulatory requirements including the following: European Commission Directive (2001/20/EC Apr 2001), and /or European Commission Directive (2005/28/EC Apr 2005), and/or European Data Protection Directive (94/46/EC), and/or General Data Protection Regulation (European Union 2016/679), and/or other applicable local regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 24 February 2017 |
| 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: 10 |
| Country: Number of subjects enrolled | Poland: 140 |
| Country: Number of subjects enrolled | Portugal: 24 |
| Country: Number of subjects enrolled | Spain: 115 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Country: Number of subjects enrolled | Austria: 26 |
| Country: Number of subjects enrolled | Belgium: 80 |
| Country: Number of subjects enrolled | France: 41 |
| Country: Number of subjects enrolled | Germany: 167 |
| Country: Number of subjects enrolled | Hungary: 103 |
| Country: Number of subjects enrolled | Lithuania: 45 |
| Country: Number of subjects enrolled | Italy: 153 |
| Country: Number of subjects enrolled | Romania: 39 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Serbia: 28 |
| Country: Number of subjects enrolled | Korea, Republic of: 91 |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Taiwan: 78 |
| Country: Number of subjects enrolled | Ukraine: 344 |
| Worldwide total number of subjects | 1506 |
| EEA total number of subjects | 958 |

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) | 428 |
| From 65 to 84 years | 1007 |
| 85 years and over | 71 |

Subject disposition

Recruitment

Recruitment details:

A total of 1506 subjects who met all inclusion criteria and no exclusion criteria were enrolled in the study; 1486 subjects received treatment. A total of 20 subjects (5 Edoxaban and 15 Vitamin K antagonist) did not receive treatment.

Pre-assignment

Screening details:

The screening period started after a percutaneous coronary intervention (PCI) with stent placement. Subjects were randomized 1:1 to either a Edoxaban-based or VKA-based regimen within 4 hours and 5 days after a successful PCI.

Period 1

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

Blinding implementation details:

This was an open-label study with blinded endpoint evaluation.

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Edoxaban Regimen |

Arm description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Edoxaban |
| Investigational medicinal product code | |
| Other name | Savaysa |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

60 mg once-daily or 30 mg once-daily, oral administration

| | |
|--|--------------------|
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code | |
| Other name | Plavix |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Clopidogrel 75 mg once daily

| | |
|--|--------------------|
| Investigational medicinal product name | Prasugrel |
| Investigational medicinal product code | |
| Other name | Effient |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Prasugrel 5 mg or 10 mg once daily

| | |
|--|------------|
| Investigational medicinal product name | Ticagrelor |
| Investigational medicinal product code | |
| Other name | |

| | |
|------------------------------------|--------------------|
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Ticagrelor 90 mg twice daily | |

| | |
|------------------|------------------------------|
| Arm title | Vitamin K Antagonist Regimen |
|------------------|------------------------------|

Arm description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration.

| | |
|--|----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Vitamin K antagonist |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

VKA once daily dosing for target international normalized ratio between 2.0 and 3.0, inclusive

| | |
|--|--------------------|
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code | |
| Other name | Plavix |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Clopidogrel 75 mg once daily

| | |
|--|--------------------|
| Investigational medicinal product name | Prasugrel |
| Investigational medicinal product code | |
| Other name | Effient |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Prasugrel 5 mg or 10 mg once daily

| | |
|--|--------------------|
| Investigational medicinal product name | Ticagrelor |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ticagrelor 90 mg twice daily

| Number of subjects in period 1 | Edoxaban Regimen | Vitamin K Antagonist Regimen |
|---------------------------------------|------------------|------------------------------|
| Started | 751 | 755 |
| Completed | 616 | 580 |
| Not completed | 135 | 175 |
| Consent withdrawn by subject | 31 | 52 |
| Physician decision | 3 | 15 |

| | | |
|---------------------------|----|----|
| Adverse event, non-fatal | 56 | 54 |
| Death | 30 | 23 |
| Not specified | 7 | 14 |
| Did not receive treatment | 5 | 15 |
| Progressive disease | 1 | 1 |
| Lost to follow-up | 2 | - |
| Lack of efficacy | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Edoxaban Regimen |
|-----------------------|------------------|

Reporting group description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

| | |
|-----------------------|------------------------------|
| Reporting group title | Vitamin K Antagonist Regimen |
|-----------------------|------------------------------|

Reporting group description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration).

| Reporting group values | Edoxaban Regimen | Vitamin K Antagonist Regimen | Total |
|--|------------------|------------------------------|-------|
| Number of subjects | 751 | 755 | 1506 |
| 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) | 226 | 202 | 428 |
| From 65-84 years | 489 | 518 | 1007 |
| 85 years and over | 36 | 35 | 71 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 69.4 | 70.1 | - |
| standard deviation | ± 9.74 | ± 9.51 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 194 | 192 | 386 |
| Male | 557 | 563 | 1120 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Romania | 17 | 22 | 39 |
| Hungary | 49 | 54 | 103 |
| Ukraine | 169 | 175 | 344 |
| United Kingdom | 6 | 9 | 15 |
| Portugal | 12 | 12 | 24 |
| Switzerland | 2 | 5 | 7 |
| Spain | 58 | 57 | 115 |
| Austria | 18 | 8 | 26 |
| Netherlands | 3 | 7 | 10 |
| South Korea | 50 | 41 | 91 |
| Belgium | 43 | 37 | 80 |

| | | | |
|-----------|----|----|-----|
| Taiwan | 32 | 46 | 78 |
| Poland | 74 | 66 | 140 |
| Italy | 69 | 84 | 153 |
| France | 21 | 20 | 41 |
| Lithuania | 24 | 21 | 45 |
| Serbia | 17 | 11 | 28 |
| Germany | 87 | 80 | 167 |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Edoxaban Regimen |
| Reporting group description: Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used). | |
| Reporting group title | Vitamin K Antagonist Regimen |
| Reporting group description: Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration). | |

Primary: Number of Participants With Adjudicated Major or Clinically Relevant Non-major Bleeding As First Event Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

| | |
|---|--|
| End point title | Number of Participants With Adjudicated Major or Clinically Relevant Non-major Bleeding As First Event Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen ^[1] |
| End point description: Subjects' first major or clinically relevant non-major bleeding (MCRB) events were reported. International Society on Thrombosis and Hemostasis (ISTH) defined bleeding events included: MCRB, major bleeding, including fatal bleeding (intracranial and non-intracranial), symptomatic intracranial hemorrhage, symptomatic bleeding in a critical area or organ, and clinically overt and causing ≥ 2.0 g/dL adjusted hemoglobin loss, clinically relevant non-major (CRNM) bleeding, minor bleedings, any bleeding (defined as the composite of major, CRNM, and minor bleeding), life-threatening bleeding, provoked (spontaneous, instrumental/traumatic, unknown) bleeding, and spontaneous bleeding. | |
| End point type | Primary |
| End point timeframe: Day 1 to 12 months postdose | |

Notes:

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

Justification: Descriptive analyses were performed based on the study groups and the study drugs administered for this outcome.

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|--|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 751 | 755 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Composite MCRB | 128 | 152 | | |
| Major bleeding | 39 | 44 | | |
| Clinically relevant non-major bleeding | 89 | 108 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Major, Clinically Relevant Non-major and Minor Bleeding (All Events) Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist-Based Regimen

| | |
|-----------------|---|
| End point title | Number of Participants With Adjudicated Major, Clinically Relevant Non-major and Minor Bleeding (All Events) Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist-Based Regimen |
|-----------------|---|

End point description:

All major, clinically relevant non-major and minor bleeding are reported for the secondary outcome. Subjects may have experiences more than 1 bleeding event, all occurrences are reported. Subjects with International Society on Thrombosis and Hemostasis (ISTH) defined bleeding events included: major or clinically relevant non-major bleeding (MCRB), major bleeding, including fatal bleeding (intracranial and non-intracranial), symptomatic intracranial hemorrhage, symptomatic bleeding in a critical area or organ, and clinically overt and causing ≥ 2.0 g/dL adjusted hemoglobin loss, clinically relevant non-major (CRNM) bleeding, minor bleedings, any bleeding (defined as the composite of major, CRNM, and minor bleeding), life-threatening bleeding, provoked (spontaneous, instrumental/traumatic, unknown) bleeding, and spontaneous bleeding.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to 12 months postdose

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|--|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 751 | 755 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Major bleeding | 45 | 48 | | |
| Clinically relevant non-major bleeding | 97 | 114 | | |
| Minor bleeding | 116 | 125 | | |
| Symptomatic intracranial hemorrhage | 4 | 9 | | |
| Fatal major bleeding | 1 | 7 | | |
| Fatal intracranial hemorrhage | 0 | 4 | | |
| Life-threatening bleeding | 5 | 8 | | |
| Spontaneous bleeding | 184 | 210 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Major, Minor, and Minimal Bleeding by Thrombolysis in Myocardial Infarction (TIMI) Definition Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

| | |
|-----------------|---|
| End point title | Number of Participants With Adjudicated Major, Minor, and |
|-----------------|---|

End point description:

Thrombolysis in Myocardial Infarction (TIMI) defined bleeding events included: Major bleeding (including fatal bleeding and non-fatal bleeding [fulfilling the TIMI major bleeding definition], major or minor bleeding, minor bleeding, minimal bleeding, and any bleeding (defined as composite of major, minor, and minimal bleeding)

End point type Secondary

End point timeframe:

Day 1 to 12 months postdose

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|-----------------------------|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 751 | 755 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Major bleeding | 15 | 24 | | |
| Fatal bleeding | 1 | 4 | | |
| Major or minor bleeding | 124 | 144 | | |
| Minor bleeding | 113 | 126 | | |
| Minimal bleeding | 117 | 131 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Bleeding Academic Research Consortium (BARC) Type 1, 2, 3, and 5 Bleeding According to the BARC Definitions Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)- Based Regimen

| | |
|-----------------|--|
| End point title | Number of Participants With Bleeding Academic Research Consortium (BARC) Type 1, 2, 3, and 5 Bleeding According to the BARC Definitions Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)- Based Regimen |
|-----------------|--|

End point description:

Bleeding Academic Research Consortium (BARC) bleeding events included: Bleeding (defined by BARC type 3 or 5), bleeding (defined by BARC type 2, 3, or 5), and any bleeding (defined as the composite of BARC type 1, 2, 3, or 5), where increases in BARC type indicate worse outcome. Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consultation; Type 2: any overt, actionable sign of hemorrhage that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation; Type 3: Overt bleeding plus hemoglobin drop of 3 to ≤ 5 g/dL (3a), ≥ 5 g/dL (3b), and intracranial hemorrhage (3c) Type 5: Fatal bleeding

End point type Secondary

End point timeframe:

Day 1 to 12 months postdose

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|------------------------------------|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 751 | 755 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Bleeding (BARC Type 3 or 5) | 36 | 42 | | |
| Bleeding (BARC Type 2, 3 or 5) | 124 | 144 | | |
| Bleeding (BARC Type 1, 2, 3, or 5) | 207 | 242 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen |
|-----------------|---|

End point description:

Treatment-emergent adverse events (TEAEs) in >1.0% of subjects were defined as events which started on or after first dose of the assigned study drug (edoxaban and VKA) or started prior to but then worsened after the first dose of the assigned study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to 30 days after the last dose

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|-----------------------------|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 746 | 740 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Any TEAE | 457 | 447 | | |
| Infections and Infestations | 145 | 140 | | |
| Nasopharyngitis | 25 | 22 | | |
| Pneumonia | 20 | 22 | | |
| Bronchitis | 19 | 20 | | |
| Urinary tract infection | 14 | 19 | | |
| Respiratory tract infection | 12 | 15 | | |
| Influenza | 10 | 7 | | |
| Cardiac Disorders | 136 | 134 | | |

| | | | | |
|---|-----|----|--|--|
| Cardiac failure | 40 | 47 | | |
| Atrial fibrillation | 39 | 41 | | |
| Bradycardia | 10 | 7 | | |
| Cardiac failure congestive | 8 | 8 | | |
| Ventricular extrasystoles | 7 | 8 | | |
| Tachycardia | 11 | 3 | | |
| General Disorders & Administration Site Condition | 113 | 98 | | |
| Non-cardiac chest pain | 30 | 24 | | |
| Oedema peripheral | 31 | 22 | | |
| Asthenia | 21 | 14 | | |
| Chest pain | 7 | 11 | | |
| Fatigue | 11 | 6 | | |
| Gastrointestinal Disorders | 110 | 83 | | |
| Diarrhea | 23 | 19 | | |
| Constipation | 11 | 7 | | |
| Abdominal pain upper | 6 | 10 | | |
| Gastritis | 9 | 5 | | |
| Nausea | 8 | 5 | | |
| Dyspepsia | 8 | 3 | | |
| Respiratory, Thoracic, and Mediastinal Disorders | 87 | 72 | | |
| Dyspnoea | 22 | 26 | | |
| Cough | 21 | 11 | | |
| Dyspnoea exertional | 18 | 5 | | |
| Chronic obstructive pulmonary disease | 6 | 10 | | |
| Musculoskeletal and Connective Tissue Disorders | 69 | 83 | | |
| Back pain | 14 | 14 | | |
| Arthralgia | 11 | 12 | | |
| Pain in extremity | 5 | 13 | | |
| Myalgia | 8 | 8 | | |
| Osteoarthritis | 9 | 5 | | |
| Investigations | 70 | 79 | | |
| Blood creatinine increased | 15 | 13 | | |
| Alanine aminotransferase increased | 8 | 13 | | |
| Blood pressure increased | 12 | 8 | | |
| Creatinine renal clearance decreased | 12 | 7 | | |
| Aspartate aminotransferase increased | 7 | 11 | | |
| International normalized ratio increased | 0 | 12 | | |
| Nervous System Disorders | 83 | 65 | | |
| Dizziness | 30 | 22 | | |
| Headache | 19 | 12 | | |
| Syncope | 8 | 6 | | |
| Vascular Disorders | 55 | 62 | | |
| Hypertension | 23 | 23 | | |
| Hypotension | 14 | 14 | | |
| Hypertensive crisis | 11 | 8 | | |
| Renal and Urinary Disorders | 49 | 55 | | |
| Renal failure | 11 | 12 | | |
| Acute kidney injury | 8 | 13 | | |
| Renal impairment | 7 | 8 | | |

| | | | | |
|---|----|----|--|--|
| Injury, Poisoning, and Procedural Complications | 44 | 44 | | |
| Fall | 8 | 12 | | |
| Skin and Subcutaneous Tissue Disorders | 55 | 33 | | |
| Pruritus | 12 | 7 | | |
| Rash | 10 | 9 | | |
| Metabolism and Nutrition Disorders | 42 | 42 | | |
| Gout | 11 | 4 | | |
| Blood and Lymphatic System Disorders | 41 | 35 | | |
| Anaemia | 19 | 20 | | |
| Psychiatric Disorder | 23 | 20 | | |
| Insomnia | 8 | 8 | | |
| Ear and Labyrinth Disorders | 12 | 16 | | |
| Vertigo | 8 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Study Drug-related Treatment-emergent Adverse Events (TEAEs) Experienced by 2 or More Subjects Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

| | |
|-----------------|--|
| End point title | Number of Subjects With Study Drug-related Treatment-emergent Adverse Events (TEAEs) Experienced by 2 or More Subjects Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen |
|-----------------|--|

End point description:

Study drug-related treatment-emergent adverse events (TEAEs) (experienced by 2 or more subjects) were defined as events which started on or after first dose of the assigned study drug (edoxaban and VKA) or started prior to but then worsened after the first dose of the assigned study drug and were found to be related to treatment by the Investigator.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to 30 days after the last dose

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|--|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 746 | 740 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Any Related TEAE | 57 | 48 | | |
| Blood and Lymphatic System Disorders | 12 | 11 | | |
| Anaemia | 9 | 7 | | |
| Haemorrhagic anaemia | 0 | 2 | | |
| Normochromic normocytic anaemia | 2 | 0 | | |
| Investigations | 7 | 16 | | |
| International normalised ratio increased | 0 | 12 | | |

| | | | | |
|--|----|---|--|--|
| Blood creatinine increased | 3 | 1 | | |
| Creatinine renal clearance decreased | 2 | 2 | | |
| Haemoglobin decreased | 2 | 0 | | |
| Gastrointestinal Disorders | 12 | 4 | | |
| Abdominal pain upper | 3 | 1 | | |
| Dyspepsia | 3 | 1 | | |
| Nausea | 2 | 0 | | |
| Skin and Subcutaneous Tissue Disorders | 6 | 5 | | |
| Pruritus | 2 | 1 | | |
| Rash | 1 | 2 | | |
| Injury, Poisoning, and Procedural Complications | 1 | 7 | | |
| Overdose | 0 | 4 | | |
| Contusion | 1 | 1 | | |
| General Disorders & Administration Site Conditions | 6 | 1 | | |
| Death | 3 | 0 | | |
| Renal and Urinary Disorders | 2 | 2 | | |
| Chronic kidney disease | 1 | 1 | | |
| Renal failure | 1 | 1 | | |
| Nervous System Disorders | 3 | 0 | | |
| Dizziness | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Main Efficacy Endpoints For the Overall Study Period Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

| | |
|------------------------|---|
| End point title | Number of Participants With Main Efficacy Endpoints For the Overall Study Period Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen |
| End point description: | The main efficacy endpoints were defined as the composite of CV death (ARC), stroke (protocol defined), systemic embolic event (SEE), myocardial infarction (MI), or definite stent thrombosis. |
| End point type | Secondary |
| End point timeframe: | Day 1 to 12 months postdose |

| End point values | Edoxaban Regimen | Vitamin K Antagonist Regimen | | |
|-----------------------------|------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 751 | 755 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Composite MEE event | 49 | 46 | | |
| Cardiovascular death (ARC) | 10 | 12 | | |

| | | | | |
|------------------------------|----|----|--|--|
| Stroke (Protocol definition) | 10 | 11 | | |
| Systemic embolic event | 0 | 0 | | |
| Myocardial infarction | 22 | 18 | | |
| Definite stent thrombosis | 7 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Day 1 to 30 days after last dose, up to 2 years, 4 months.

Adverse event reporting additional description:

Adverse events were reported from the Safety Analysis Set (746 Edoxaban regimen; 740 Vitamin K Antagonist regimen).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Edoxaban Regimen |
|-----------------------|------------------|

Reporting group description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

| | |
|-----------------------|------------------------------|
| Reporting group title | Vitamin K Antagonist Regimen |
|-----------------------|------------------------------|

Reporting group description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration).

| Serious adverse events | Edoxaban Regimen | Vitamin K Antagonist Regimen | |
|---|--------------------|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 176 / 746 (23.59%) | 175 / 740 (23.65%) | |
| number of deaths (all causes) | 46 | 37 | |
| number of deaths resulting from adverse events | 29 | 24 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical fibroxanthoma | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibrosarcoma | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophageal carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic neoplasm | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectosigmoid cancer | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue neoplasm malignant stage unspecified | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 4 / 746 (0.54%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Coronary revascularisation | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| 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 | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Death | | | |
| subjects affected / exposed | 4 / 746 (0.54%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 2 / 4 | 0 / 3 | |
| Drowning | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hernia | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 6 / 746 (0.80%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Vascular stent restenosis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent thrombosis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Immune system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Amyloidosis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spermatocele | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary edema | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 5 / 746 (0.67%) | 9 / 740 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea at rest | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device capturing issue | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Injury, poisoning and procedural complications | | | |
| Arterial restenosis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compression fracture | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Costal cartilage fracture | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (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 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hip fracture | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product use issue | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound necrosis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Phimosis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Cardiac disorders | | | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adams-Stokes syndrome | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 20 / 746 (2.68%) | 14 / 740 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 29 / 746 (3.89%) | 35 / 740 (4.73%) | |
| occurrences causally related to treatment / all | 0 / 29 | 4 / 35 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 4 / 740 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 6 / 746 (0.80%) | 5 / 740 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Carotid artery stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervicogenic headache | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoparesis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| 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 / 746 (0.54%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrogenic anaemia | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Normochromic normocytic anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal stenosis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal polyp | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary fistula | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 746 (0.40%) | 4 / 740 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (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 | | | |
| Cold sweat | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigoid | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoriasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 7 / 740 (0.95%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 746 (0.67%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Chondropathy | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 3 / 740 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monarthritis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathic arthropathy | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatic disorder | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Aeromonas infection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device-related infection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site infection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious colitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (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 | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis cryptococcal | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal abscess | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 14 / 746 (1.88%) | 13 / 740 (1.76%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 3 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 746 (0.27%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 746 (0.40%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Sialoadenitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| 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 | 3 / 746 (0.40%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 746 (0.13%) | 0 / 740 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 746 (0.27%) | 2 / 740 (0.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 0 / 746 (0.00%) | 1 / 740 (0.14%) | |
| 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 / 746 (0.00%) | 1 / 740 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Edoxaban Regimen | Vitamin K Antagonist Regimen | |
|---|--------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 457 / 746 (61.26%) | 447 / 740 (60.41%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 23 / 746 (3.08%) | 23 / 740 (3.11%) | |
| occurrences (all) | 23 | 23 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 11 / 746 (1.47%) | 8 / 740 (1.08%) | |
| occurrences (all) | 11 | 8 | |
| Hypotension | | | |
| subjects affected / exposed | 14 / 746 (1.88%) | 14 / 740 (1.89%) | |
| occurrences (all) | 14 | 14 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 21 / 746 (2.82%) | 14 / 740 (1.89%) | |
| occurrences (all) | 21 | 14 | |
| Chest pain | | | |
| subjects affected / exposed | 7 / 746 (0.94%) | 11 / 740 (1.49%) | |
| occurrences (all) | 7 | 11 | |
| Fatigue | | | |

| | | | |
|---|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 11 / 746 (1.47%) 11 | 6 / 740 (0.81%) 6 | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 30 / 746 (4.02%) 30 | 24 / 740 (3.24%) 24 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 31 / 746 (4.16%) 31 | 22 / 740 (2.97%) 22 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 6 / 746 (0.80%) 6 | 10 / 740 (1.35%) 10 | |
| Cough subjects affected / exposed occurrences (all) | 21 / 746 (2.82%) 21 | 11 / 740 (1.49%) 11 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 22 / 746 (2.95%) 22 | 26 / 740 (3.51%) 26 | |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 18 / 746 (2.41%) 18 | 5 / 740 (0.68%) 5 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 8 / 740 (1.08%) 8 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 13 / 740 (1.76%) 13 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 746 (0.94%) 7 | 11 / 740 (1.49%) 11 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 15 / 746 (2.01%) 15 | 13 / 740 (1.76%) 13 | |

| | | | |
|--|------------------------|------------------------|--|
| Blood pressure increased subjects affected / exposed occurrences (all) | 12 / 746 (1.61%) 12 | 8 / 740 (1.08%) 8 | |
| Creatinine renal clearance increased subjects affected / exposed occurrences (all) | 12 / 746 (1.61%) 12 | 7 / 740 (0.95%) 7 | |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 0 / 746 (0.00%) 0 | 12 / 740 (1.62%) 12 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 12 / 740 (1.62%) 12 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 39 / 746 (5.23%) 39 | 41 / 740 (5.54%) 41 | |
| Bradycardia subjects affected / exposed occurrences (all) | 10 / 746 (1.34%) 10 | 7 / 740 (0.95%) 7 | |
| Cardiac failure subjects affected / exposed occurrences (all) | 40 / 746 (5.36%) 40 | 47 / 740 (6.35%) 47 | |
| Cardiac failure congestive subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 8 / 740 (1.08%) 8 | |
| Tachycardia subjects affected / exposed occurrences (all) | 11 / 746 (1.47%) 11 | 3 / 740 (0.41%) 3 | |
| Ventricular extrasystoles subjects affected / exposed occurrences (all) | 7 / 746 (0.94%) 7 | 8 / 740 (1.08%) 8 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 30 / 746 (4.02%) 30 | 22 / 740 (2.97%) 22 | |

| | | | |
|--|------------------------|------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 19 / 746 (2.55%) 19 | 12 / 740 (1.62%) 12 | |
| Syncope subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 6 / 740 (0.81%) 6 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 19 / 746 (2.55%) 19 | 20 / 740 (2.70%) 20 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 5 / 740 (0.68%) 5 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 6 / 746 (0.80%) 6 | 10 / 740 (1.35%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 11 / 746 (1.47%) 11 | 7 / 740 (0.95%) 7 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 23 / 746 (3.08%) 23 | 19 / 740 (2.57%) 19 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 3 / 740 (0.41%) 3 | |
| Gastritis subjects affected / exposed occurrences (all) | 9 / 746 (1.21%) 9 | 5 / 740 (0.68%) 5 | |
| Nausea subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 5 / 740 (0.68%) 5 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 12 / 746 (1.61%) 12 | 7 / 740 (0.95%) 7 | |

| | | | |
|---|------------------------|------------------------|--|
| Rash subjects affected / exposed occurrences (all) | 10 / 746 (1.34%) 10 | 9 / 740 (1.22%) 9 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 13 / 740 (1.76%) 13 | |
| Renal failure subjects affected / exposed occurrences (all) | 11 / 746 (1.47%) 11 | 12 / 740 (1.62%) 12 | |
| Renal impairment subjects affected / exposed occurrences (all) | 7 / 746 (0.94%) 7 | 8 / 740 (1.08%) 8 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 11 / 746 (1.47%) 11 | 12 / 740 (1.62%) 12 | |
| Back pain subjects affected / exposed occurrences (all) | 14 / 746 (1.88%) 14 | 14 / 740 (1.89%) 14 | |
| Myalgia subjects affected / exposed occurrences (all) | 8 / 746 (1.07%) 8 | 8 / 740 (1.08%) 8 | |
| Osteoarthritis subjects affected / exposed occurrences (all) | 9 / 746 (1.21%) 9 | 5 / 740 (0.68%) 5 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 746 (0.67%) 5 | 13 / 740 (1.76%) 13 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 19 / 746 (2.55%) 19 | 20 / 740 (2.70%) 20 | |
| Influenza subjects affected / exposed occurrences (all) | 10 / 746 (1.34%) 10 | 7 / 740 (0.95%) 7 | |

| | | | |
|------------------------------------|------------------|------------------|--|
| Nasopharyngitis | | | |
| subjects affected / exposed | 25 / 746 (3.35%) | 22 / 740 (2.97%) | |
| occurrences (all) | 25 | 22 | |
| Pneumonia | | | |
| subjects affected / exposed | 20 / 746 (2.68%) | 22 / 740 (2.97%) | |
| occurrences (all) | 20 | 22 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 12 / 746 (1.61%) | 15 / 740 (2.03%) | |
| occurrences (all) | 12 | 15 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 14 / 746 (1.88%) | 19 / 740 (2.57%) | |
| occurrences (all) | 14 | 19 | |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 11 / 746 (1.47%) | 4 / 740 (0.54%) | |
| occurrences (all) | 11 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 09 January 2017 | Updated secondary exploratory objectives, study design, and subject eligibility criteria; amended the procedure for removing subjects from therapy; revised procedures prior to and following randomization; clarified assessments to be performed at each site; and included a definition of unexpected adverse events. |
| 28 February 2017 | Updated exclusion criteria for subjects with renal impairment and end stage renal disease. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported