



Clinical trial results:

A PHASE 2, RANDOMIZED, PARALLEL GROUP, DOSE-FINDING, MULTICENTER, MULTINATIONAL STUDY OF THE SAFETY, TOLERABILITY AND PILOT EFFICACY OF THREE BLINDED DOSES OF THE ORAL FACTOR Xa INHIBITOR BETRIXABAN COMPARED WITH OPEN- LABEL, DOSE-ADJUSTED WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2008-005977-37 |
| Trial protocol | DE |
| Global end of trial date | 05 November 2009 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 28 December 2017 |
| First version publication date | 28 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 08-015 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00742859 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Portola Pharmaceuticals, Inc. |
| Sponsor organisation address | 270 East Grand Avenue, South San Francisco, United States, 94080 |
| Public contact | Janice Castillo, Portola Pharmaceuticals, Inc., 001 650-246-7360, |
| Scientific contact | Janice Castillo, Portola Pharmaceuticals, Inc., 001 650-246-7360, |

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 | 18 July 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 August 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 November 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to assess the safety and tolerability of betrixaban at doses of 40 mg, 60 mg and 80 mg given orally once a day for at least 3 months compared to a dose-adjusted Vitamin K antagonist in patients with non-valvular AF.

Protection of trial subjects:

The conduct of this clinical study met local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 31 October 2008 |
| 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 | Germany: 12 |
| Country: Number of subjects enrolled | United States: 369 |
| Country: Number of subjects enrolled | Canada: 127 |
| Worldwide total number of subjects | 508 |
| EEA total number of subjects | 12 |

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) | 81 |
| From 65 to 84 years | 397 |
| 85 years and over | 30 |

Subject disposition

Recruitment

Recruitment details:

Between 31 October 2008 and 05 November 2009, 508 patients were enrolled by 35 study centers in 3 countries (USA, Canada, Germany). Patients were randomized to 1 of 4 treatment groups (1:1:1:1 allocation). The study was open-label for warfarin, while the 3 daily doses of betrixaban (40, 60, or 80 mg) were double-blinded.

Pre-assignment

Screening details:

561 patients were screened for study participation. Of these patients, 508 were randomized, all of whom received at least 1 dose of study drug.

Period 1

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Betrixaban 40 mg |

Arm description:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Betrixaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|------------------|------------------|
| Arm title | Betrixaban 60 mg |
|------------------|------------------|

Arm description:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Betrixaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|------------------|------------------|
| Arm title | Betrixaban 80 mg |
|------------------|------------------|

Arm description:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Betrixaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|------------------|----------|
| Arm title | Warfarin |
|------------------|----------|

Arm description:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Warfarin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

| Number of subjects in period 1 | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg |
|--|------------------|------------------|------------------|
| Started | 127 | 127 | 127 |
| Completed | 116 | 115 | 116 |
| Not completed | 11 | 12 | 11 |
| Adverse event, serious fatal | 1 | - | - |
| Consent withdrawn by subject | 4 | 2 | 4 |
| Physician decision | 1 | 2 | - |
| Amendment 2 Pt off Study Drug for >4 weeks | - | 1 | 1 |
| Adverse event, non-fatal | 5 | 6 | 3 |
| Sponsor request visit schedule noncompliance | - | - | - |
| Sponsor request PT out of town | - | - | 1 |
| Site Error | - | - | 1 |
| Endpoint | - | 1 | 1 |

| Number of subjects in period 1 | Warfarin |
|---------------------------------------|----------|
| Started | 127 |
| Completed | 119 |
| Not completed | 8 |
| Adverse event, serious fatal | 1 |

| | |
|--|---|
| Consent withdrawn by subject | 1 |
| Physician decision | - |
| Amendment 2 Pt off Study Drug for >4 weeks | - |
| Adverse event, non-fatal | 1 |
| Sponsor request visit schedule noncompliance | 1 |
| Sponsor request PT out of town | 1 |
| Site Error | 1 |
| Endpoint | 2 |

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Betrixaban 40 mg |
| Reporting group description: Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Betrixaban 60 mg |
| Reporting group description: Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Betrixaban 80 mg |
| Reporting group description: Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Warfarin |
| Reporting group description: Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months | |

| Reporting group values | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg |
|---|------------------|------------------|------------------|
| Number of subjects | 127 | 127 | 127 |
| Age categorical | | | |
| All randomized patients who took at least 1 dose of study medication after randomization. | | | |
| Units: Subjects | | | |
| <=64 years | 21 | 19 | 22 |
| 65<=age<85 years | 97 | 96 | 100 |
| age >=85 years | 9 | 12 | 5 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 73.3 | 73.8 | 72.0 |
| standard deviation | ± 8.5 | ± 8.35 | ± 7.65 |
| Gender categorical | | | |
| All randomized patients who took at least 1 dose of study medication after randomization. | | | |
| Units: Subjects | | | |
| Female | 79 | 81 | 89 |
| Male | 48 | 46 | 38 |

| Reporting group values | Warfarin | Total | |
|---|----------|-------|--|
| Number of subjects | 127 | 508 | |
| Age categorical | | | |
| All randomized patients who took at least 1 dose of study medication after randomization. | | | |
| Units: Subjects | | | |
| <=64 years | 19 | 81 | |
| 65<=age<85 years | 104 | 397 | |

| | | | |
|----------------|---|----|--|
| age >=85 years | 4 | 30 | |
|----------------|---|----|--|

| | | | |
|---|--------|-----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 72.7 | | |
| standard deviation | ± 8.75 | - | |
| Gender categorical | | | |
| All randomized patients who took at least 1 dose of study medication after randomization. | | | |
| Units: Subjects | | | |
| Female | 89 | 338 | |
| Male | 38 | 170 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Betrixaban 40 mg |
| Reporting group description: Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Betrixaban 60 mg |
| Reporting group description: Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Betrixaban 80 mg |
| Reporting group description: Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months | |
| Reporting group title | Warfarin |
| Reporting group description: Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months | |

Primary: Exposure-adjusted incidence rate of major or clinically relevant non-major bleeding episode

| | |
|---|---|
| End point title | Exposure-adjusted incidence rate of major or clinically relevant non-major bleeding episode |
| End point description: The primary endpoint is the time to the first occurrence of major or clinically relevant non-major bleeding. This was presented as the exposure adjusted incidence rate which was calculated as number of subjects experiencing the event divided by total person years across all subjects, where if a patient experiencing the event, year was from first dose date to the first occurrence of the event, and to last study date if not. The confidence interval was calculated via the exact Poisson distribution. | |
| End point type | Primary |
| End point timeframe: A maximum of 1 year | |

| End point values | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg | Warfarin |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 127 | 127 | 127 | 127 |
| Units: Number of Participants | | | | |
| number (confidence interval 95%) | 2.02 (0.05 to 11.3) | 10.1 (3.28 to 23.6) | 10.5 (3.41 to 24.5) | 14.6 (5.85 to 30.0) |

Statistical analyses

| | |
|--|-----------------------------|
| Statistical analysis title | Betrixaban 40 mg |
| Statistical analysis description: | |
| Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution. | |
| Comparison groups | Warfarin v Betrixaban 40 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.035 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.017 |
| upper limit | 1.14 |

| | |
|---|-----------------------------|
| Statistical analysis title | Betrixaban 60 mg |
| Comparison groups | Warfarin v Betrixaban 60 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.546 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.711 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.225 |
| upper limit | 2.24 |

| | |
|---|-----------------------------|
| Statistical analysis title | Betrixaban 80 mg |
| Comparison groups | Warfarin v Betrixaban 80 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.712 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.755 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.239 |
| upper limit | 2.39 |

Secondary: Exposure-adjusted incidence rate of any bleeding (major, clinically relevant non-major, or minimal)

| | |
|-----------------|---|
| End point title | Exposure-adjusted incidence rate of any bleeding (major, clinically relevant non-major, or minimal) |
|-----------------|---|

End point description:

The time to the first occurrence of any bleeding event. This was presented as the exposure adjusted incidence rate which was calculated as number of subjects experiencing the event divided by total person years across all subjects, where if a patient experiencing the event, year was from first dose date to the first occurrence of the event, and to last study date if not. The confidence interval was calculated via the exact Poisson distribution.

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

End point timeframe:

A maximum of 1 year

| End point values | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg | Warfarin |
|---|---------------------|--------------------|---------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 127 | 127 | 127 | 127 |
| Units: number of patients per 100 patient years | | | | |
| number (confidence interval 95%) | 50.5 (31.7 to 76.5) | 77.9 (53.3 to 110) | 56.0 (35.9 to 83.4) | 103 (73.6 to 140) |

Statistical analyses

| | |
|----------------------------|------------------|
| Statistical analysis title | Betrixaban 40 mg |
|----------------------------|------------------|

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

| | |
|---|-----------------------------|
| Comparison groups | Warfarin v Betrixaban 40 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.011 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.508 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.301 |
| upper limit | 0.856 |

| | |
|-----------------------------------|------------------|
| Statistical analysis title | Betrixaban 60 mg |
|-----------------------------------|------------------|

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

| | |
|---|-----------------------------|
| Comparison groups | Warfarin v Betrixaban 60 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.308 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.767 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.481 |
| upper limit | 1.22 |

| | |
|-----------------------------------|------------------|
| Statistical analysis title | Betrixaban 80 mg |
|-----------------------------------|------------------|

Statistical analysis description:

Incidence rate indicating the number of patients reporting events per 100 patient years. 95% CI was calculated via exact method assuming Poisson distribution.

| | |
|---|-----------------------------|
| Comparison groups | Warfarin v Betrixaban 80 mg |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.022 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.551 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.332 |
| upper limit | 0.914 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date (including) till the end of study

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Betrixaban 40 mg |
|-----------------------|------------------|

Reporting group description:

Betrixaban 40 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|-----------------------|------------------|
| Reporting group title | Betrixaban 60 mg |
|-----------------------|------------------|

Reporting group description:

Betrixaban 60 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|-----------------------|------------------|
| Reporting group title | Betrixaban 80 mg |
|-----------------------|------------------|

Reporting group description:

Betrixaban 80 mg once daily for at least 3 months and no longer than approximately 11 months

| | |
|-----------------------|----------|
| Reporting group title | Warfarin |
|-----------------------|----------|

Reporting group description:

Dose-adjusted warfarin to maintain an INR of 2.0 to 3.0 with INR measured at maximum intervals of 4 weeks. Treatment duration was at least 3 months and no longer than approximately 11 months

| Serious adverse events | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 127 (9.45%) | 12 / 127 (9.45%) | 11 / 127 (8.66%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac neoplasm unspecified | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer recurrent | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatic obstruction | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 127 (0.79%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Fall | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 127 (0.79%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Grand mal convulsion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia obstructive | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament disorder | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 0 / 127 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Warfarin | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 127 (9.45%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac neoplasm unspecified | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon cancer recurrent | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Lung neoplasm malignant subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cancer subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders Deep vein thrombosis subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions Chest pain subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders Prostatic obstruction subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar radiculopathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal hernia obstructive | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|--|--|
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament disorder | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Betrixaban 40 mg | Betrixaban 60 mg | Betrixaban 80 mg |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 127 (48.03%) | 68 / 127 (53.54%) | 53 / 127 (41.73%) |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 4 / 127 (3.15%) | 0 / 127 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | 3 / 127 (2.36%) | 1 / 127 (0.79%) |
| occurrences (all) | 3 | 3 | 1 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
| occurrences (all) | 2 | 0 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 12 / 127 (9.45%) | 9 / 127 (7.09%) | 6 / 127 (4.72%) |
| occurrences (all) | 12 | 11 | 6 |
| Headache | | | |
| subjects affected / exposed | 5 / 127 (3.94%) | 6 / 127 (4.72%) | 9 / 127 (7.09%) |
| occurrences (all) | 6 | 6 | 9 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 5 / 127 (3.94%) | 1 / 127 (0.79%) | 2 / 127 (1.57%) |
| occurrences (all) | 5 | 1 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 7 / 127 (5.51%) | 5 / 127 (3.94%) | 4 / 127 (3.15%) |
| occurrences (all) | 7 | 6 | 4 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 127 (6.30%) | 10 / 127 (7.87%) | 6 / 127 (4.72%) |
| occurrences (all) | 8 | 11 | 7 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|-----------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 2 | 5 / 127 (3.94%) 5 | 2 / 127 (1.57%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 9 / 127 (7.09%) 10 | 8 / 127 (6.30%) 8 | 3 / 127 (2.36%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | 10 / 127 (7.87%) 11 | 9 / 127 (7.09%) 11 |
| Dyspepsia subjects affected / exposed occurrences (all) | 7 / 127 (5.51%) 7 | 0 / 127 (0.00%) 0 | 4 / 127 (3.15%) 4 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 2 | 5 / 127 (3.94%) 5 | 14 / 127 (11.02%) 15 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | 2 / 127 (1.57%) 2 | 6 / 127 (4.72%) 6 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | 8 / 127 (6.30%) 8 | 3 / 127 (2.36%) 3 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | 3 / 127 (2.36%) 3 | 5 / 127 (3.94%) 5 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | 3 / 127 (2.36%) 3 | 3 / 127 (2.36%) 3 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 3 | 4 / 127 (3.15%) 4 | 5 / 127 (3.94%) 5 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 5 | 6 / 127 (4.72%) 6 | 3 / 127 (2.36%) 3 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Back pain subjects affected / exposed occurrences (all) | 5 / 127 (3.94%) 5 | 6 / 127 (4.72%) 6 | 6 / 127 (4.72%) 6 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | 2 / 127 (1.57%) 2 | 4 / 127 (3.15%) 4 |
| Influenza subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 2 | 1 / 127 (0.79%) 1 | 4 / 127 (3.15%) 4 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 127 (3.94%) 6 | 5 / 127 (3.94%) 5 | 3 / 127 (2.36%) 4 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 127 (3.94%) 7 | 1 / 127 (0.79%) 1 | 4 / 127 (3.15%) 4 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | 1 / 127 (0.79%) 1 | 2 / 127 (1.57%) 3 |

| | | | |
|--|----------------------|--|--|
| Non-serious adverse events | Warfarin | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 50 / 127 (39.37%) | | |
| Investigations | | | |
| Liver function test abnormal subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| Vascular disorders | | | |
| Hypertension subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | | |
| Cardiac disorders | | | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| General disorders and administration site conditions | | | |
| Chest pain subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| Fatigue subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 11 / 127 (8.66%) 12 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 2 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--|--|--|
| Cough subjects affected / exposed occurrences (all) | 3 / 127 (2.36%) 3 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 127 (1.57%) 2 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 127 (0.79%) 1 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 127 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 4 / 127 (3.15%) 4 2 / 127 (1.57%) 2 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection | 0 / 127 (0.00%) 0 1 / 127 (0.79%) 1 10 / 127 (7.87%) 11 3 / 127 (2.36%) 3 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 127 (3.15%) | | |
| occurrences (all) | 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 30 October 2008 | <ul style="list-style-type: none">•Investigational site was added & PI was added to Steering Committee•Drug packaging change from blister pack to bottle capsules•Modification of Inclusion and Exclusion Criteria•Modification of lab samples collected•Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency. |
| 06 May 2009 | <ul style="list-style-type: none">•Modification of Inclusion and Exclusion Criteria•Allowed flexibility with drug dosing time•Modification of lab samples collected•Endpoint Definitions were added•Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported