



## Clinical trial results: Efficacy of citalopram treatment in acute stroke Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-002253-30   |
| Trial protocol           | DK               |
| Global end of trial date | 19 December 2016 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 29 November 2021 |
| First version publication date | 29 November 2021 |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 2011/397 |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01937182 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Aarhus University   |
| Sponsor organisation address | Nordre Ringgade 1, Aarhus, Denmark, 8000  |
| Public contact               | Department of Neurology, Aarhus University Hospital, +45 89493294, greander@rm.dk |
| Scientific contact           | Department of Neurology, Aarhus University Hospital, +45 89493294, greander@rm.dk |

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                       | 10 May 2017      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 19 December 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 December 2016 |
| Was the trial ended prematurely?                     | No               |

---

Notes:

---

## General information about the trial

---

Main objective of the trial:

To examine whether citalopram treatment in acute stroke reduces the risk of combined death, re-stroke and myocardial infarction

---

Protection of trial subjects:

Patients, or their proxy respondent, provided written informed consent before enrollment.

If patients develop depression dosage is initially doubled, followed by an additional control to evaluate the effect and, if necessary, shifted to open-label antidepressant treatment. After six-months, treatment will either stop or switch to open-label antidepressants at the discretion of the investigator.

Exclusion criteria included:

- Moderate to severe dementia or other neurodegenerative diseases
  - Patient on antidepressant medication within one month prior to admission
  - Contraindications to citalopram
  - Indication, in the clinician's view, for antidepressant medication therapy
  - History of abuse or other circumstances deeming follow-up not possible
  - Actively bleeding ulcers
  - Fatal stroke or significant co-morbidity, resulting in an expected short life span
  - Pregnant or breast-feeding women
- 

Background therapy:

Patients included in the trial were treated in accordance with international best medical and surgical guidelines. All patients received standard care for stroke, including reperfusion therapy (ie, intravenous r-tPA (recombinant tissue-type plasminogen activator ) or endovascular treatment), if indicated.

---

Evidence for comparator:

Some small or single-blinded placebo-controlled studies using a selective serotonin reuptake inhibitor (SSRI), and in particular, the FLAME study (Fluoxetine for Motor Recovery After Acute Ischemic Stroke) in 2011 gave rise to optimism. FLAME was a double-blinded randomized study, including 118 patients with moderate to severe stroke and showed increased motor recovery after 3 months of rehabilitation with SSRI treatment. A recent large study of escitalopram on prevention of poststroke depression found no improved functional outcome at 3 months (secondary outcome).

Various theories have been suggested for a possible beneficial effect of SSRI treatment including a neurotrophic effect, increased neurogenesis and proliferation, an anti-inflammatory effect, protein expression enhancement, upregulation of 31-adrenergic receptors, or simply prevention or treatment of depression and anxiety, and improved sleep and alertness.

In addition, a large observational study (n=5833) in propensity score-matched ischemic stroke patients has indicated a lower long-term risk of recurrent cardiovascular events associated with SSRI treatment. Treatment with SSRI has also been associated with increased bleeding problems; therefore, the safety and a potential antithrombotic effect must be considered when used in the subacute phase after stroke. A potential antithrombotic effect is a plausible effect of SSRI treatment owing to platelet inhibition, for example, by lowering the concentration of platelet serotonin or via the platelet-activating P2Y12-receptor.

---

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 01 August 2013 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

---

### Population of trial subjects

---

#### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Denmark: 642 |
| Worldwide total number of subjects   | 642          |
| EEA total number of subjects         | 642          |

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)                      | 237 |
| From 65 to 84 years                       | 347 |
| 85 years and over                         | 58  |

## Subject disposition

### Recruitment

Recruitment details:

Consecutive patients were enrolled in Denmark from 1 highly specialized stroke center (Aarhus) and 2 primary stroke units (Aalborg and Glostrup). Glostrup). The first and the last patient were recruited on September 17, 2013, and June 27, 2016, respectively. The last follow-up was performed on December 19, 2016.

### Pre-assignment

Screening details:

Patients who were  $\geq 18$  years of age with first-ever ischemic stroke onset (ie, last known to be free of stroke symptoms) within the previous 7 days were eligible for inclusion. A total of 949 patients were screened, 642 of which were included.

### Period 1

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

Blinding implementation details:

Treatment allocation is double-blinded and allocated in a 10-block design based on computer-generated algorithm via a dedicated website. Patients whose treatment is stopped within 31 days after inclusion will be replaced.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Patients allocated to placebo

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

Dosage and administration details:

Patients randomized to placebo received oral treatment with 1 tablet (0,5 when age  $\geq 65$  and/or reduced liver function) for six-months with telephone contact after two-weeks and three-months and follow-up visits at one- and six-months. Treatment was initiated as soon as possible and no later than seven days after symptom onset. If patients developed depression dosage was initially doubled, followed by an additional control to evaluate the effect and, if necessary, shifted to open-label antidepressant treatment. After six-months, treatment was either stopped or switched to open-label antidepressants at the discretion of the investigator.

|                  |        |
|------------------|--------|
| <b>Arm title</b> | Active |
|------------------|--------|

Arm description:

Patients allocated to citalopram

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

---

Dosage and administration details:

Initial dose: 20 mg orally once a day

Maintenance dose: 20 to 40 mg orally once a day

Maximum dose: 40 mg orally per day

| <b>Number of subjects in period 1</b> | Placebo | Active |
|---------------------------------------|---------|--------|
| Started                               | 323     | 319    |
| Completed                             | 284     | 268    |
| Not completed                         | 39      | 51     |
| Consent withdrawn by subject          | 14      | 29     |
| Physician decision                    | 9       | 10     |
| Adverse event, non-fatal              | 4       | 6      |
| Indication for open label treatment   | 12      | 6      |

## Baseline characteristics

### Reporting groups

|  |         |
|--|---------|
| Reporting group title  | Placebo |
| Reporting group description:<br>Patients allocated to placebo    |         |
| Reporting group title  | Active  |
| Reporting group description:<br>Patients allocated to citalopram |         |

| Reporting group values                                | Placebo | Active | Total |
|---|---------|--------|-------|
| Number of subjects                                    | 323     | 319    | 642   |
| Age categorical                                       |         |        |       |
| Units: Subjects                                       |         |        |       |
| In utero  | 0       | 0      | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0      | 0     |
| Newborns (0-27 days)                                  | 0       | 0      | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0       | 0      | 0     |
| Children (2-11 years)                                 | 0       | 0      | 0     |
| Adolescents (12-17 years)                             | 0       | 0      | 0     |
| Adults (18-64 years)                                  | 123     | 114    | 237   |
| From 65-84 years                                      | 167     | 180    | 347   |
| 85 years and over                                     | 33      | 25     | 58    |
| Age continuous  |         |        |       |
| Units: years  |         |        |       |
| arithmetic mean                                       | 68.36   | 68.24  |       |
| standard deviation                                    | ± 12.8  | ± 12.5 | -     |
| Gender categorical                                    |         |        |       |
| Units: Subjects                                       |         |        |       |
| Female  | 101     | 120    | 221   |
| Male  | 222     | 199    | 421   |

## End points

### End points reporting groups

|                                  |         |
|----------------------------------|---------|
| Reporting group title            | Placebo |
| Reporting group description:     |         |
| Patients allocated to placebo    |         |
| Reporting group title            | Active  |
| Reporting group description:     |         |
| Patients allocated to citalopram |         |

### Primary: Improvement in functional disability

|   |                                      |
|---|--------------------------------------|
| End point title   | Improvement in functional disability |
| End point description:  |                                      |
| Improvement in functional disability from 1 to 6 months, as measured by the modified Rankin Scale (mRS) |                                      |
| End point type  | Primary                              |
| End point timeframe:  |                                      |
| 6 months  |                                      |

| End point values             | Placebo            | Active             |  |  |
|------------------------------|--------------------|--------------------|--|--|
| Subject group type           | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed  | 284 <sup>[1]</sup> | 268 <sup>[2]</sup> |  |  |
| Units: modified Rankin Scale |                    |                    |  |  |
| number (not applicable)      |                    |                    |  |  |
| mRS                          | 160                | 136                |  |  |

Notes:

[1] - Placebo

[2] - Citalopram

### Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Improvement in functional disability |
| Comparison groups                       | Placebo v Active                     |
| Number of subjects included in analysis | 552                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | > 0.05                               |
| Method                                  | t-test, 2-sided                      |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1.37                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.97                                 |
| upper limit                             | 1.91                                 |

|                      |                    |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
|----------------------|--------------------|

### Primary: Composite vascular end point

|   |                              |
|---|------------------------------|
| End point title   | Composite vascular end point |
| End point description:<br>A composite vascular end point of TIA/stroke (ischemic and hemorrhagic), MI, or vascular mortality during the first 6 months. Registry-based follow-up was obtained from patients discontinuing study medication before 6 months. |                              |
| End point type  | Primary                      |
| End point timeframe:<br>6 months  |                              |

| End point values             | Placebo            | Active             |  |  |
|------------------------------|--------------------|--------------------|--|--|
| Subject group type           | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed  | 323 <sup>[3]</sup> | 319 <sup>[4]</sup> |  |  |
| Units: Number of events      |                    |                    |  |  |
| TIA/stroke, MI and mortality | 26                 | 23                 |  |  |

Notes:

[3] - Placebo

[4] - Citalopram

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | The vascular coprimary end point occurred |
| Comparison groups                       | Placebo v Active                          |
| Number of subjects included in analysis | 642                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | < 0.05                                    |
| Method                                  | Fisher exact                              |
| Parameter estimate                      | Hazard ratio (HR)                         |
| Point estimate                          | 0.89                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.5                                       |
| upper limit                             | 1.74                                      |
| Variability estimate                    | Standard deviation                        |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

6 months according to the protocol, or as long as the patients were included.

Adverse event reporting additional description:

AE reporting were performed non-systematically for the duration of patient inclusion in the project. Death reporting were done systematically in a intention-to-treat approach with all deaths within 6 months after inclusion reported.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Active |
|-----------------------|--------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| <b>Serious adverse events</b>  | Active   | Placebo           |  |
|--|--|-------------------|--|
| Total subjects affected by serious adverse events                                      |  |                   |  |
| subjects affected / exposed  | 66 / 319 (20.69%)  | 75 / 323 (23.22%) |  |
| number of deaths (all causes)  | 16   | 12                |  |
| number of deaths resulting from adverse events   | 6  | 5                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                    |  |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps): Carcinoma In Situ | Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps): Carcinoma In Situ |                   |  |
| subjects affected / exposed  | 3 / 319 (0.94%)  | 2 / 323 (0.62%)   |  |
| occurrences causally related to treatment / all  | 0 / 3  | 0 / 2             |  |
| deaths causally related to treatment / all   | 0 / 1  | 0 / 0             |  |
| Vascular disorders   |  |                   |  |
| Vascular disorders: New Extremity Ischemia   | Additional description: Vascular disorders: New Extremity Ischemia   |                   |  |
| subjects affected / exposed  | 1 / 319 (0.31%)  | 1 / 323 (0.31%)   |  |
| occurrences causally related to treatment / all  | 0 / 1  | 0 / 1             |  |
| deaths causally related to treatment / all   | 0 / 0  | 0 / 0             |  |
| Vascular disorders: Peripheral Vascular – Other (Specify)                              | Additional description: Vascular disorders: Peripheral Vascular – Other (Specify)                              |                   |  |

|  |                 |                  |  |
|--|-----------------|------------------|--|
| subjects affected / exposed  | 1 / 319 (0.31%) | 0 / 323 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| <b>Surgical and medical procedures</b>   |                 |                  |  |
| Additional description: Surgical and medical procedures: Carotid Endarectomy                               |                 |                  |  |
| subjects affected / exposed  | 2 / 319 (0.63%) | 1 / 323 (0.31%)  |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| Additional description: Surgical and medical procedures: Other, specify                                    |                 |                  |  |
| subjects affected / exposed  | 1 / 319 (0.31%) | 0 / 323 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| Additional description: Surgical and medical procedures: Surgery – Other (Specify)                         |                 |                  |  |
| subjects affected / exposed  | 8 / 319 (2.51%) | 12 / 323 (3.72%) |  |
| occurrences causally related to treatment / all  | 0 / 8           | 0 / 12           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>   |                 |                  |  |
| Additional description: Respiratory, thoracic and mediastinal disorders: Respiratory - Other (Specify)     |                 |                  |  |
| subjects affected / exposed  | 0 / 319 (0.00%) | 2 / 323 (0.62%)  |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| Additional description: Respiratory, thoracic and mediastinal disorders: Respiratory Insufficiency/Failure |                 |                  |  |
| subjects affected / exposed  | 0 / 319 (0.00%) | 1 / 323 (0.31%)  |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| <b>Psychiatric disorders</b>   |                 |                  |  |
| Additional description: Psychiatric disorders: Depression  |                 |                  |  |
| subjects affected / exposed  | 0 / 319 (0.00%) | 1 / 323 (0.31%)  |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0            |  |
| Additional description: Psychiatric disorders: Other, specify  |                 |                  |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                                    | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 2  | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Psychiatric disorders: Psychiatric - Other (Specify)           | Additional description: Psychiatric disorders: Psychiatric - Other (Specify)           |                 |  |
| subjects affected / exposed                                    | 1 / 319 (0.31%)  | 6 / 323 (1.86%) |  |
| occurrences causally related to treatment / all                | 0 / 1  | 0 / 6           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Investigations   | Additional description: Investigations: Biochemical - Low Plasma Sodium Concentration  |                 |  |
| Investigations: Biochemical - Low Plasma Sodium Concentration  | Additional description: Investigations: Biochemical - Low Plasma Sodium Concentration  |                 |  |
| subjects affected / exposed                                    | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Investigations: Paraclinical - Other (Specify)                 | Additional description: Investigations: Paraclinical - Other (Specify)                 |                 |  |
| subjects affected / exposed                                    | 4 / 319 (1.25%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                | 0 / 4  | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Injury, poisoning and procedural complications                 | Additional description: Injury, poisoning and procedural complications: Other, specify |                 |  |
| Injury, poisoning and procedural complications: Other, specify | Additional description: Injury, poisoning and procedural complications: Other, specify |                 |  |
| subjects affected / exposed                                    | 3 / 319 (0.94%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 3  | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Cardiac disorders  | Additional description: Cardiac disorders: ACS: Myocardial Infarction - NSTEMI         |                 |  |
| Cardiac disorders: ACS: Myocardial Infarction - NSTEMI         | Additional description: Cardiac disorders: ACS: Myocardial Infarction - NSTEMI         |                 |  |
| subjects affected / exposed                                    | 2 / 319 (0.63%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                | 0 / 2  | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 1           |  |
| Cardiac disorders: Arrhythmia - Other (Specify)                | Additional description: Cardiac disorders: Arrhythmia - Other (Specify)                |                 |  |
| subjects affected / exposed                                    | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Arrhythmia - Severe                         | Additional description: Cardiac disorders: Arrhythmia - Severe                         |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed   | 2 / 319 (0.63%)   | 2 / 323 (0.62%) |  |
| occurrences causally related to treatment / all                                     | 0 / 2   | 0 / 2           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Atrial Fibrillation  | Additional description: Cardiac disorders: Atrial Fibrillation  |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                                     | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Cardiac Ischemia - Other (Specify)                               | Additional description: Cardiac disorders: Cardiac Ischemia - Other (Specify)                               |                 |  |
| subjects affected / exposed   | 1 / 319 (0.31%)   | 2 / 323 (0.62%) |  |
| occurrences causally related to treatment / all                                     | 0 / 1   | 0 / 2           |  |
| deaths causally related to treatment / all  | 0 / 1   | 0 / 1           |  |
| Cardiac disorders: Cardiovascular - Other (Specify)                                 | Additional description: Cardiac disorders: Cardiovascular - Other (Specify)                                 |                 |  |
| subjects affected / exposed   | 1 / 319 (0.31%)   | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                                     | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Chest Pain   | Additional description: Cardiac disorders: Chest Pain   |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 2 / 323 (0.62%) |  |
| occurrences causally related to treatment / all                                     | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Electrocardiogram - Other Abnormal Findings (Specify)            | Additional description: Cardiac disorders: Electrocardiogram - Other Abnormal Findings (Specify)            |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                                     | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Endovascular Or Surgical Intervention - Planned (Specify Site)   | Additional description: Cardiac disorders: Endovascular Or Surgical Intervention - Planned (Specify Site)   |                 |  |
| subjects affected / exposed   | 5 / 319 (1.57%)   | 5 / 323 (1.55%) |  |
| occurrences causally related to treatment / all                                     | 0 / 5   | 0 / 5           |  |
| deaths causally related to treatment / all  | 0 / 0   | 0 / 0           |  |
| Cardiac disorders: Endovascular Or Surgical Intervention - Unplanned (Specify Site) | Additional description: Cardiac disorders: Endovascular Or Surgical Intervention - Unplanned (Specify Site) |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed  | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                        | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Heart Failure – Other (Specify)                     | Additional description: Cardiac disorders: Heart Failure – Other (Specify)                     |                 |  |
| subjects affected / exposed  | 2 / 319 (0.63%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                        | 0 / 2  | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Left Ventricular Insufficiency (Specify NYHA-Class) | Additional description: Cardiac disorders: Left Ventricular Insufficiency (Specify NYHA-Class) |                 |  |
| subjects affected / exposed  | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                        | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Peripheral Edema                                    | Additional description: Cardiac disorders: Peripheral Edema                                    |                 |  |
| subjects affected / exposed  | 2 / 319 (0.63%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                        | 0 / 2  | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Pulmonary Edema                                     | Additional description: Cardiac disorders: Pulmonary Edema                                     |                 |  |
| subjects affected / exposed  | 1 / 319 (0.31%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                        | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Stable Angina                                       | Additional description: Cardiac disorders: Stable Angina                                       |                 |  |
| subjects affected / exposed  | 0 / 319 (0.00%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                        | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Syncope – cardiovascular                            | Additional description: Cardiac disorders: Syncope – cardiovascular                            |                 |  |
| subjects affected / exposed  | 1 / 319 (0.31%)  | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                        | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |
| Cardiac disorders: Tachycardia – Sinus                                 | Additional description: Cardiac disorders: Tachycardia – Sinus                                 |                 |  |
| subjects affected / exposed  | 0 / 319 (0.00%)  | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                        | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0  | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Nervous system disorders  |                 |                 |  |
| Additional description: Nervous system disorders: Delirium                                  |                 |                 |  |
| Nervous system disorders: Delirium<br>subjects affected / exposed                           | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Additional description: Nervous system disorders: Disabling Stroke - Haemorrhagic           |                 |                 |  |
| Nervous system disorders: Disabling<br>Stroke - Haemorrhagic<br>subjects affected / exposed | 1 / 319 (0.31%) | 0 / 323 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Additional description: Nervous system disorders: Disabling Stroke - Ischemic               |                 |                 |  |
| Nervous system disorders: Disabling<br>Stroke - Ischemic<br>subjects affected / exposed     | 3 / 319 (0.94%) | 1 / 323 (0.31%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 3           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 2           | 0 / 0           |  |
| Additional description: Nervous system disorders: Dizziness - non-cardiovascular            |                 |                 |  |
| Nervous system disorders: Dizziness<br>- non-cardiovascular<br>subjects affected / exposed  | 1 / 319 (0.31%) | 1 / 323 (0.31%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Additional description: Nervous system disorders: Headache                                  |                 |                 |  |
| Nervous system disorders: Headache<br>subjects affected / exposed                           | 1 / 319 (0.31%) | 3 / 323 (0.93%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 3           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Additional description: Nervous system disorders: Neurological - Other (Specify)            |                 |                 |  |
| Nervous system disorders:<br>Neurological - Other (Specify)<br>subjects affected / exposed  | 1 / 319 (0.31%) | 2 / 323 (0.62%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Additional description: Nervous system disorders: Neurovascular - Other (Specify)           |                 |                 |  |
| Nervous system disorders:<br>Neurovascular - Other (Specify)<br>subjects affected / exposed | 1 / 319 (0.31%) | 1 / 323 (0.31%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 1           | 0 / 1           |  |
| Additional description: Nervous system disorders: Non-Disabling Stroke - Haemorrhagic       |                 |                 |  |
| Nervous system disorders: Non-<br>Disabling Stroke - Haemorrhagic                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 1 / 319 (0.31%) | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Nervous system disorders: Non-Disabling Stroke – Ischemic                         |                 |                 |  |
| Additional description: Nervous system disorders: Non-Disabling Stroke – Ischemic |                 |                 |  |
| subjects affected / exposed   | 3 / 319 (0.94%) | 8 / 323 (2.48%) |  |
| occurrences causally related to treatment / all                                   | 0 / 3           | 0 / 8           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Nervous system disorders: Other, specify  |                 |                 |  |
| Additional description: Nervous system disorders: Other, specify                  |                 |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                                   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Nervous system disorders: Seizure   |                 |                 |  |
| Additional description: Nervous system disorders: Seizure                         |                 |                 |  |
| subjects affected / exposed   | 1 / 319 (0.31%) | 2 / 323 (0.62%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Nervous system disorders: Subarachnoid hemorrhage (SAH)                           |                 |                 |  |
| Additional description: Nervous system disorders: Subarachnoid hemorrhage (SAH)   |                 |                 |  |
| subjects affected / exposed   | 1 / 319 (0.31%) | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all                                   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| Nervous system disorders: Syncope – non-cardiovascular                            |                 |                 |  |
| Additional description: Nervous system disorders: Syncope – non-cardiovascular    |                 |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                                   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Nervous system disorders: Transient Ischemic Attack (TIA)                         |                 |                 |  |
| Additional description: Nervous system disorders: Transient Ischemic Attack (TIA) |                 |                 |  |
| subjects affected / exposed   | 5 / 319 (1.57%) | 7 / 323 (2.17%) |  |
| occurrences causally related to treatment / all                                   | 0 / 5           | 0 / 8           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders  |                 |                 |  |
| Additional description: Blood and lymphatic system disorders: Anaemia             |                 |                 |  |
| Blood and lymphatic system disorders: Anaemia                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>   |                 |                 |  |
| Additional description: Gastrointestinal disorders: Diarrhoea   |                 |                 |  |
| Gastrointestinal disorders: Diarrhoea subjects affected / exposed                                       | 1 / 319 (0.31%) | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Additional description: Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)                 |                 |                 |  |
| Gastrointestinal disorders: Gastro-Intestinal - Other (Specify) subjects affected / exposed             | 3 / 319 (0.94%) | 5 / 323 (1.55%) |  |
| occurrences causally related to treatment / all   | 0 / 5           | 0 / 6           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| <b>Renal and urinary disorders</b>  |                 |                 |  |
| Additional description: Renal and urinary disorders: Biochemical - Renal Dysfunction                    |                 |                 |  |
| Renal and urinary disorders: Biochemical - Renal Dysfunction subjects affected / exposed                | 1 / 319 (0.31%) | 0 / 323 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Additional description: Renal and urinary disorders: Urinary And Genital Organs - Other (Specify)       |                 |                 |  |
| Renal and urinary disorders: Urinary And Genital Organs - Other (Specify) subjects affected / exposed   | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| <b>Endocrine disorders</b>  |                 |                 |  |
| Additional description: Endocrine disorders: Diabetes   |                 |                 |  |
| Endocrine disorders: Diabetes subjects affected / exposed   | 0 / 319 (0.00%) | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Additional description: Endocrine disorders: Endocrine, nutritional and metabolic - Other (Specify)     |                 |                 |  |
| Endocrine disorders: Endocrine, nutritional and metabolic - Other (Specify) subjects affected / exposed | 0 / 319 (0.00%) | 2 / 323 (0.62%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| <b>Musculoskeletal and connective tissue disorders</b>  |                 |                 |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Musculoskeletal and connective tissue disorders: Fall causing bone fracture | Additional description: Musculoskeletal and connective tissue disorders: Fall causing bone fracture |                 |  |
| subjects affected / exposed   | 6 / 319 (1.88%)   | 1 / 323 (0.31%) |  |
| occurrences causally related to treatment / all                             | 0 / 6   | 0 / 1           |  |
| deaths causally related to treatment / all                                  | 0 / 0   | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders: Other, specify             | Additional description: Musculoskeletal and connective tissue disorders: Other, specify             |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 3 / 323 (0.93%) |  |
| occurrences causally related to treatment / all                             | 0 / 0   | 0 / 3           |  |
| deaths causally related to treatment / all                                  | 0 / 0   | 0 / 0           |  |
| Infections and infestations   | Additional description: Infections and infestations: Infection - Other (Specify)                    |                 |  |
| Infections and infestations: Infection - Other (Specify)                    | Additional description: Infections and infestations: Infection - Other (Specify)                    |                 |  |
| subjects affected / exposed   | 5 / 319 (1.57%)   | 7 / 323 (2.17%) |  |
| occurrences causally related to treatment / all                             | 0 / 5   | 0 / 8           |  |
| deaths causally related to treatment / all                                  | 0 / 0   | 0 / 0           |  |
| Infections and infestations: Infection - Pulmonary                          | Additional description: Infections and infestations: Infection - Pulmonary                          |                 |  |
| subjects affected / exposed   | 12 / 319 (3.76%)  | 6 / 323 (1.86%) |  |
| occurrences causally related to treatment / all                             | 0 / 12  | 0 / 6           |  |
| deaths causally related to treatment / all                                  | 0 / 0   | 0 / 1           |  |
| Infections and infestations: Infection - Urinary                            | Additional description: Infections and infestations: Infection - Urinary                            |                 |  |
| subjects affected / exposed   | 2 / 319 (0.63%)   | 6 / 323 (1.86%) |  |
| occurrences causally related to treatment / all                             | 0 / 2   | 0 / 6           |  |
| deaths causally related to treatment / all                                  | 0 / 0   | 0 / 1           |  |
| Infections and infestations: Other, specify                                 | Additional description: Infections and infestations: Other, specify                                 |                 |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%) |  |
| 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: 0 %

| <b>Non-serious adverse events</b>   | Active  | Placebo            |  |
|---|---|--------------------|--|
| Total subjects affected by non-serious adverse events   |   |                    |  |
| subjects affected / exposed   | 167 / 319 (52.35%)  | 180 / 323 (55.73%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                             |   |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps): Benign Neoplasms           | Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps): Benign Neoplasms           |                    |  |
| subjects affected / exposed   | 1 / 319 (0.31%)   | 2 / 323 (0.62%)    |  |
| occurrences (all)   | 1   | 2                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps): Carcinoma In Situ          | Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps): Carcinoma In Situ          |                    |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 2 / 323 (0.62%)    |  |
| occurrences (all)   | 0   | 2                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps): Neoplasm - Other (Specify) | Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps): Neoplasm - Other (Specify) |                    |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%)    |  |
| occurrences (all)   | 0   | 1                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps): Other, specify             | Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps): Other, specify             |                    |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%)    |  |
| occurrences (all)   | 0   | 1                  |  |
| Vascular disorders  |   |                    |  |
| Vascular disorders: Other, specify  | Additional description: Vascular disorders: Other, specify  |                    |  |
| subjects affected / exposed   | 1 / 319 (0.31%)   | 1 / 323 (0.31%)    |  |
| occurrences (all)   | 1   | 1                  |  |
| Surgical and medical procedures   |   |                    |  |
| Surgical and medical procedures: Carotid Endarectomy  | Additional description: Surgical and medical procedures: Carotid Endarectomy  |                    |  |
| subjects affected / exposed   | 11 / 319 (3.45%)  | 15 / 323 (4.64%)   |  |
| occurrences (all)   | 11  | 15                 |  |
| Surgical and medical procedures: Other, specify   | Additional description: Surgical and medical procedures: Other, specify   |                    |  |
| subjects affected / exposed   | 0 / 319 (0.00%)   | 1 / 323 (0.31%)    |  |
| occurrences (all)   | 0   | 1                  |  |
| Surgical and medical procedures: Surgery - Other (Specify)                                      | Additional description: Surgical and medical procedures: Surgery - Other (Specify)                                      |                    |  |
| subjects affected / exposed   | 8 / 319 (2.51%)   | 5 / 323 (1.55%)    |  |
| occurrences (all)   | 8   | 6                  |  |
| Respiratory, thoracic and mediastinal disorders   |   |                    |  |

|  |  |                   |
|--|--|-------------------|
| Respiratory, thoracic and mediastinal disorders: Other, specify                    | Additional description: Respiratory, thoracic and mediastinal disorders: Other, specify                    |                   |
| subjects affected / exposed  | 1 / 319 (0.31%)  | 1 / 323 (0.31%)   |
| occurrences (all)  | 1  | 1                 |
| Respiratory, thoracic and mediastinal disorders: Respiratory - Other (Specify)     | Additional description: Respiratory, thoracic and mediastinal disorders: Respiratory - Other (Specify)     |                   |
| subjects affected / exposed  | 6 / 319 (1.88%)  | 4 / 323 (1.24%)   |
| occurrences (all)  | 6  | 4                 |
| Respiratory, thoracic and mediastinal disorders: Respiratory Insufficiency/Failure | Additional description: Respiratory, thoracic and mediastinal disorders: Respiratory Insufficiency/Failure |                   |
| subjects affected / exposed  | 2 / 319 (0.63%)  | 0 / 323 (0.00%)   |
| occurrences (all)  | 2  | 0                 |
| Psychiatric disorders  |  |                   |
| Psychiatric disorders: Depression  | Additional description: Psychiatric disorders: Depression  |                   |
| subjects affected / exposed  | 35 / 319 (10.97%)  | 47 / 323 (14.55%) |
| occurrences (all)  | 35   | 47                |
| Psychiatric disorders: Laugh Lability  | Additional description: Psychiatric disorders: Laugh Lability  |                   |
| subjects affected / exposed  | 0 / 319 (0.00%)  | 1 / 323 (0.31%)   |
| occurrences (all)  | 0  | 1                 |
| Psychiatric disorders: Other, specify  | Additional description: Psychiatric disorders: Other, specify  |                   |
| subjects affected / exposed  | 0 / 319 (0.00%)  | 1 / 323 (0.31%)   |
| occurrences (all)  | 0  | 1                 |
| Psychiatric disorders: Pathological Crying   | Additional description: Psychiatric disorders: Pathological Crying   |                   |
| subjects affected / exposed  | 2 / 319 (0.63%)  | 17 / 323 (5.26%)  |
| occurrences (all)  | 2  | 18                |
| Psychiatric disorders: Psychiatric - Other (Specify)                               | Additional description: Psychiatric disorders: Psychiatric - Other (Specify)                               |                   |
| subjects affected / exposed  | 8 / 319 (2.51%)  | 14 / 323 (4.33%)  |
| occurrences (all)  | 8  | 15                |
| Investigations   |  |                   |
| Investigations: Biochemical - Low Plasma Sodium Concentration                      | Additional description: Investigations: Biochemical - Low Plasma Sodium Concentration                      |                   |
| subjects affected / exposed  | 2 / 319 (0.63%)  | 2 / 323 (0.62%)   |
| occurrences (all)  | 2  | 2                 |
| Investigations: Paraclinical - Other (Specify)                                     | Additional description: Investigations: Paraclinical - Other (Specify)                                     |                   |
| subjects affected / exposed  | 9 / 319 (2.82%)  | 10 / 323 (3.10%)  |
| occurrences (all)  | 10   | 13                |

|  |  |                      |  |
|--|--|----------------------|--|
| Injury, poisoning and procedural complications   |  |                      |  |
| Injury, poisoning and procedural complications: Other, specify subjects affected / exposed           | Additional description: Injury, poisoning and procedural complications: Other, specify           |                      |  |
| occurrences (all)  | 6 / 319 (1.88%)<br>6   | 6 / 323 (1.86%)<br>6 |  |
| Cardiac disorders  |  |                      |  |
| Cardiac disorders: Arrhythmia – Major subjects affected / exposed                                    | Additional description: Cardiac disorders: Arrhythmia – Major                                    |                      |  |
| occurrences (all)  | 0 / 319 (0.00%)<br>0   | 1 / 323 (0.31%)<br>1 |  |
| Cardiac disorders: Arrhythmia – Minor subjects affected / exposed                                    | Additional description: Cardiac disorders: Arrhythmia – Minor                                    |                      |  |
| occurrences (all)  | 0 / 319 (0.00%)<br>0   | 1 / 323 (0.31%)<br>1 |  |
| Cardiac disorders: Arrhythmia – Other (Specify) subjects affected / exposed                          | Additional description: Cardiac disorders: Arrhythmia – Other (Specify)                          |                      |  |
| occurrences (all)  | 2 / 319 (0.63%)<br>2   | 1 / 323 (0.31%)<br>1 |  |
| Cardiac disorders: Atrial Fibrillation subjects affected / exposed                                   | Additional description: Cardiac disorders: Atrial Fibrillation                                   |                      |  |
| occurrences (all)  | 5 / 319 (1.57%)<br>5   | 2 / 323 (0.62%)<br>2 |  |
| Cardiac disorders: Cardiovascular – Other (Specify) subjects affected / exposed                      | Additional description: Cardiac disorders: Cardiovascular – Other (Specify)                      |                      |  |
| occurrences (all)  | 9 / 319 (2.82%)<br>10  | 6 / 323 (1.86%)<br>8 |  |
| Cardiac disorders: Chest Pain subjects affected / exposed  | Additional description: Cardiac disorders: Chest Pain  |                      |  |
| occurrences (all)  | 2 / 319 (0.63%)<br>2   | 3 / 323 (0.93%)<br>3 |  |
| Cardiac disorders: Dizziness – cardiovascular subjects affected / exposed                            | Additional description: Cardiac disorders: Dizziness – cardiovascular                            |                      |  |
| occurrences (all)  | 3 / 319 (0.94%)<br>3   | 4 / 323 (1.24%)<br>4 |  |
| Cardiac disorders: Electrocardiogram – Other Abnormal Findings (Specify) subjects affected / exposed | Additional description: Cardiac disorders: Electrocardiogram – Other Abnormal Findings (Specify) |                      |  |
| occurrences (all)  | 0 / 319 (0.00%)<br>0   | 1 / 323 (0.31%)<br>1 |  |
| Cardiac disorders: Left Ventricular Insufficiency (Specify NYHA-Class) subjects affected / exposed   | Additional description: Cardiac disorders: Left Ventricular Insufficiency (Specify NYHA-Class)   |                      |  |
| occurrences (all)  | 5 / 319 (1.57%)<br>5   | 1 / 323 (0.31%)<br>1 |  |

|   |  |                        |
|---|--|------------------------|
| Cardiac disorders: Orthoestatism<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Cardiac disorders: Orthoestatism                         |                        |
|   | 10 / 319 (3.13%)<br>10   | 10 / 323 (3.10%)<br>10 |
| Cardiac disorders: Peripheral Edema<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Cardiac disorders: Peripheral Edema                      |                        |
|   | 2 / 319 (0.63%)<br>2   | 2 / 323 (0.62%)<br>2   |
| Cardiac disorders: Stable Angina<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Cardiac disorders: Stable Angina                         |                        |
|   | 0 / 319 (0.00%)<br>0   | 1 / 323 (0.31%)<br>1   |
| Cardiac disorders: Tachycardia –<br>Sinus<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Cardiac disorders: Tachycardia – Sinus                   |                        |
|   | 1 / 319 (0.31%)<br>1   | 1 / 323 (0.31%)<br>1   |
| Cardiac disorders: Syncope –<br>cardiovascular<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Cardiac disorders: Syncope – cardiovascular              |                        |
|   | 4 / 319 (1.25%)<br>4   | 4 / 323 (1.24%)<br>4   |
| Nervous system disorders  |  |                        |
| Nervous system disorders: Dizziness<br>– non-cardiovascular<br>subjects affected / exposed<br>occurrences (all) | Additional description: Nervous system disorders: Dizziness – non-cardiovascular |                        |
|   | 1 / 319 (0.31%)<br>1   | 2 / 323 (0.62%)<br>2   |
| Nervous system disorders:<br>Neurological - Other (Specify)<br>subjects affected / exposed<br>occurrences (all) | Additional description: Nervous system disorders: Neurological - Other (Specify) |                        |
|   | 15 / 319 (4.70%)<br>17   | 13 / 323 (4.02%)<br>13 |
| Nervous system disorders: Headache<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: Nervous system disorders: Headache                       |                        |
|   | 9 / 319 (2.82%)<br>9   | 13 / 323 (4.02%)<br>13 |
| Nervous system disorders: Other,<br>specify<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Nervous system disorders: Other, specify                 |                        |
|   | 0 / 319 (0.00%)<br>0   | 1 / 323 (0.31%)<br>1   |
| Nervous system disorders: Seizure<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Nervous system disorders: Seizure                        |                        |
|   | 2 / 319 (0.63%)<br>2   | 1 / 323 (0.31%)<br>1   |
| Blood and lymphatic system disorders  |  |                        |
| Blood and lymphatic system<br>disorders: Anaemia  | Additional description: Blood and lymphatic system disorders: Anaemia            |                        |

|   |   |                         |  |
|---|---|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 319 (0.31%)<br>1  | 3 / 323 (0.93%)<br>3    |  |
| Ear and labyrinth disorders<br>Ear and labyrinth disorders: Other, specify  | Additional description: Ear and labyrinth disorders: Other, specify                                     |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 0 / 319 (0.00%)<br>0  | 3 / 323 (0.93%)<br>3    |  |
| Eye disorders<br>Eye disorders: Other, specify  | Additional description: Eye disorders: Other, specify   |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 1 / 319 (0.31%)<br>1  | 4 / 323 (1.24%)<br>6    |  |
| Gastrointestinal disorders<br>Gastrointestinal disorders: Diarrhoea   | Additional description: Gastrointestinal disorders: Diarrhoea   |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 11 / 319 (3.45%)<br>11  | 9 / 323 (2.79%)<br>10   |  |
| Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)   | Additional description: Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)                 |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 44 / 319 (13.79%)<br>48   | 38 / 323 (11.76%)<br>54 |  |
| Skin and subcutaneous tissue disorders<br>Skin and subcutaneous tissue disorders: Mild To Moderate Bruising Or Ecchymosis | Additional description: Skin and subcutaneous tissue disorders: Mild To Moderate Bruising Or Ecchymosis |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 2 / 319 (0.63%)<br>2  | 1 / 323 (0.31%)<br>1    |  |
| Skin and subcutaneous tissue disorders: Skin - Other (Specify)  | Additional description: Skin and subcutaneous tissue disorders: Skin - Other (Specify)                  |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 6 / 319 (1.88%)<br>7  | 8 / 323 (2.48%)<br>8    |  |
| Skin and subcutaneous tissue disorders: Sweating  | Additional description: Skin and subcutaneous tissue disorders: Sweating                                |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 6 / 319 (1.88%)<br>6  | 3 / 323 (0.93%)<br>3    |  |
| Renal and urinary disorders<br>Renal and urinary disorders: Urinary And Genital Organs - Other (Specify)                  | Additional description: Renal and urinary disorders: Urinary And Genital Organs - Other (Specify)       |                         |  |
| subjects affected / exposed<br>occurrences (all)  | 16 / 319 (5.02%)<br>16  | 7 / 323 (2.17%)<br>7    |  |
| Endocrine disorders<br>Endocrine disorders: Diabetes  | Additional description: Endocrine disorders: Diabetes   |                         |  |

|   |   |                  |  |
|---|---|------------------|--|
| subjects affected / exposed   | 0 / 319 (0.00%)   | 3 / 323 (0.93%)  |  |
| occurrences (all)   | 0   | 3                |  |
| Endocrine disorders: Endocrine, nutritional and metabolic – Other (Specify) | Additional description: Endocrine disorders: Endocrine, nutritional and metabolic – Other (Specify) |                  |  |
| subjects affected / exposed   | 4 / 319 (1.25%)   | 2 / 323 (0.62%)  |  |
| occurrences (all)   | 4   | 2                |  |
| Musculoskeletal and connective tissue disorders                             | Additional description: Musculoskeletal and connective tissue disorders: Fall causing bone fracture |                  |  |
| Musculoskeletal and connective tissue disorders: Fall causing bone fracture |   |                  |  |
| subjects affected / exposed   | 1 / 319 (0.31%)   | 0 / 323 (0.00%)  |  |
| occurrences (all)   | 1   | 0                |  |
| Musculoskeletal and connective tissue disorders: Other, specify             | Additional description: Musculoskeletal and connective tissue disorders: Other, specify             |                  |  |
| subjects affected / exposed   | 8 / 319 (2.51%)   | 7 / 323 (2.17%)  |  |
| occurrences (all)   | 8   | 7                |  |
| Infections and infestations   | Additional description: Infections and infestations: Infection – Gastrointestinal                   |                  |  |
| Infections and infestations: Infection – Gastrointestinal                   |   |                  |  |
| subjects affected / exposed   | 2 / 319 (0.63%)   | 1 / 323 (0.31%)  |  |
| occurrences (all)   | 2   | 1                |  |
| Infections and infestations: Infection – Other (Specify)                    | Additional description: Infections and infestations: Infection – Other (Specify)                    |                  |  |
| subjects affected / exposed   | 6 / 319 (1.88%)   | 10 / 323 (3.10%) |  |
| occurrences (all)   | 6   | 10               |  |
| Infections and infestations: Infection – Pulmonary                          | Additional description: Infections and infestations: Infection – Pulmonary                          |                  |  |
| subjects affected / exposed   | 4 / 319 (1.25%)   | 3 / 323 (0.93%)  |  |
| occurrences (all)   | 4   | 3                |  |
| Infections and infestations: Infection – Urinary                            | Additional description: Infections and infestations: Infection – Urinary                            |                  |  |
| subjects affected / exposed   | 17 / 319 (5.33%)  | 16 / 323 (4.95%) |  |
| occurrences (all)   | 18  | 16               |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported

---

### **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/30355209>