



## 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
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#### 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:

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## 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:

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## General information about the trial

Main objective of the trial:

To examine wheather 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 P2Y<sub>12</sub>-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). 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
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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

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**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:	
Patients allocated to placebo	
Reporting group title	Active
Reporting group description:	
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 (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	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

Statistical analysis title	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
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### Primary: Composite vascular end point

End point title	Composite vascular end point
End point description: 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: 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Active
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	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	
Surgical and medical procedures			
Surgical and medical procedures: Carotid Endarectomy	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	
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	
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	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders: Respiratory - Other (Specify)	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	
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	
Psychiatric disorders			
Psychiatric disorders: Depression	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	
Psychiatric disorders: Other, specify			
	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			
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			
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			
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			
Nervous system disorders: Delirium	Additional description: Nervous system disorders: Delirium		
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: Disabling Stroke – Haemorrhagic	Additional description: Nervous system disorders: 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: Disabling Stroke – Ischemic	Additional description: Nervous system disorders: Disabling Stroke – Ischemic		
subjects affected / exposed	3 / 319 (0.94%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Nervous system disorders: Dizziness – non-cardiovascular	Additional description: Nervous system disorders: Dizziness – non-cardiovascular		
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	
Nervous system disorders: Headache	Additional description: Nervous system disorders: Headache		
subjects affected / exposed	1 / 319 (0.31%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders: Neurological - Other (Specify)	Additional description: Nervous system disorders: Neurological - 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 / 0	0 / 0	
Nervous system disorders: Neurovascular - Other (Specify)	Additional description: Nervous system disorders: Neurovascular - 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 / 1	0 / 1	
Nervous system disorders: Non-Disabling Stroke – Haemorrhagic	Additional description: Nervous system disorders: Non-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			
Blood and lymphatic system disorders: Anaemia	Additional description: 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	
Gastrointestinal disorders			
Gastrointestinal disorders: Diarrhoea	Additional description: 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	
Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)	Additional description: 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	
Renal and urinary disorders			
Renal and urinary disorders: Biochemical - Renal Dysfunction	Additional description: 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	
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	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	
Endocrine disorders			
Endocrine disorders: Diabetes	Additional description: 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	
Endocrine disorders: Endocrine, nutritional and metabolic - Other (Specify)	Additional description: 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	
Musculoskeletal and connective tissue disorders			



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			
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 %

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

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

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

subjects affected / exposed occurrences (all)	1 / 319 (0.31%) 1	3 / 323 (0.93%) 3	
Ear and labyrinth disorders Ear and labyrinth disorders: Other, specify	Additional description: Ear and labyrinth disorders: Other, specify		
subjects affected / exposed occurrences (all)	0 / 319 (0.00%) 0	3 / 323 (0.93%) 3	
Eye disorders Eye disorders: Other, specify	Additional description: Eye disorders: Other, specify		
subjects affected / exposed occurrences (all)	1 / 319 (0.31%) 1	4 / 323 (1.24%) 6	
Gastrointestinal disorders Gastrointestinal disorders: Diarrhoea	Additional description: Gastrointestinal disorders: Diarrhoea		
subjects affected / exposed occurrences (all)	11 / 319 (3.45%) 11	9 / 323 (2.79%) 10	
Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)	Additional description: Gastrointestinal disorders: Gastro-Intestinal - Other (Specify)		
subjects affected / exposed occurrences (all)	44 / 319 (13.79%) 48	38 / 323 (11.76%) 54	
Skin and subcutaneous tissue disorders 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 occurrences (all)	2 / 319 (0.63%) 2	1 / 323 (0.31%) 1	
Skin and subcutaneous tissue disorders: Skin - Other (Specify)	Additional description: Skin and subcutaneous tissue disorders: Skin - Other (Specify)		
subjects affected / exposed occurrences (all)	6 / 319 (1.88%) 7	8 / 323 (2.48%) 8	
Skin and subcutaneous tissue disorders: Sweating	Additional description: Skin and subcutaneous tissue disorders: Sweating		
subjects affected / exposed occurrences (all)	6 / 319 (1.88%) 6	3 / 323 (0.93%) 3	
Renal and urinary disorders 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 occurrences (all)	16 / 319 (5.02%) 16	7 / 323 (2.17%) 7	
Endocrine disorders 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			
Musculoskeletal and connective tissue disorders: Fall causing bone fracture	Additional description: 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			
Infections and infestations: Infection – Gastrointestinal	Additional description: 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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