Clinical trial results:
Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial, a randomized, double blind, multicentre clinical trial

Summary

EudraCT number	2013-001185-41
Trial protocol	GB ES DE FI
Global end of trial date	28 March 2018

Results information

Result version number	v1 (current)
This version publication date	10 April 2019
First version publication date	10 April 2019
Summary attachment (see zip file)	Clopidogrel and Aspirin in Acute Ischemic Stroke and High Risk TIA (nejmoa1800410[1].pdf)

Trial information

Trial identification

Sponsor protocol code	POINT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00991029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of California, San Francisco Stroke Sciences Group
Sponsor organisation address	Department of Neurology, SSG, San Francisco, United States, 94143
Public contact	Kelley Rosborough, Emmes, 1 3012511161, krosborough@emmes.com
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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	09 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2018
Global end of trial reached?	Yes
Global end of trial date	28 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether clopidogrel 75mg/day by mouth after an initial dose of 600mg, is effective in improving events related to stroke at 90 days, in patients receiving aspirin 50-325mg/day when randomized within 12 hours of time last known free of new stroke symptoms.

Protection of trial subjects:

The greatest risk to subject health was the study medication, clopidogrel, when combined with aspirin. These agents had not been tested specifically after TIA and minor ischemic stroke, so rates of hemorrhage were estimated from studies of stroke and acute coronary syndromes. All subjects in the study received aspirin. The benefits of aspirin outweigh its small excess risk of systemic and intracranial hemorrhage.

Clopidogrel in combination with aspirin is likely to be associated with a small excess risk of major systemic hemorrhage (estimated at 1% for the study period) but no increased risk of life-threatening or intracranial hemorrhage. The absolute increase in risk of life-threatening hemorrhage in the MATCH trial, which is most similar to POINT, was 1.3% (2.6% for the combination vs. 1.3% for clopidogrel alone), and this risk was spread out over 18 months follow-up. Subjects were followed for 90 days and only TIAs and minor ischemic strokes were included, so a 1% excess absolute risk was realistic,
and consistent with other trials. The combination may increase the risk of complications with interventions, such as endarterectomy, or may delay the performance of these procedures due to concerns about bleeding risk. Clopidogrel is also associated with a very small risk of thrombotic thrombocytopenic purpura, probably less than 1 per 100,000.

Loss of privacy due to additional contact from investigators not involved directly in the subject’s care was
another potential risk. There was also a small risk of loss of confidentiality.

Background therapy:

Platelet aggregation is an important contributing factor in cerebral ischemia, as in other forms of ischemia. Antiplatelet agents reduce the risk of ischemic stroke in a variety of settings with distinct pathophysiologies (e.g., atrial fibrillation, small-vessel stroke, and large-vessel atherothrombosis). Aspirin given to patients with a history of stroke or TIA reduces subsequent risk of stroke. Furthermore, aspirin initiated as an acute intervention after stroke reduces risk of death and recurrent stroke. Trials of clopidogrel in combination with aspirin after stroke/TIA suggest that the combination reduces risk of stroke but increases risk of major hemorrhage. However, the risk of thrombosis is extremely high in the acute period after TIA and risk of hemorrhage is expected to be lower than after a completed stroke, so the combination may be particularly effective and relatively safe in this setting. Even more compelling, clopidogrel combined with aspirin reduced the 90-day risk of stroke by 36% compared to aspirin alone in a pilot trial of 392 patients treated acutely after minor stroke or TIA, and it was well tolerated. Clopidogrel also has advantages in being oral, without major side effects other than hemorrhage, and it will be inexpensive by trial completion. Nonetheless, antiplatelet therapy has never been tested in a pivotal trial as an acute intervention after TIA, a setting with distinct pathophysiology that may favor the use of this class of agents.

TIA is a unique, important type of cerebral ischemia characterized by substantial instability, in which acute treatment is potentially highly consequential and has never been properly studied. Currently, the treatment choice ranges from immediate hospitalization and initiation of intravenous antiplatelet agents or heparin to outpatient evaluation and treatment with aspirin.

Evidence for comparator:

Clopidogrel has been studied in combination with aspirin in several trials of vascular disease, including

two that included patients with stroke or TIA. Although results from these trials have not supported long-term use of clopidogrel after stroke/TIA, the drug has never been tested as an acute therapy in this population and the trials support that it may be more beneficial and particularly safe after TIA. It is also a logical agent to test because it is cheap, has well established, favorable pharmacodynamics and safety profile, and is delivered conveniently in the outpatient setting.
Aspirin and clopidogrel synergistically antagonize platelet aggregation, and combined, may provide added benefit in stroke prevention. Aspirin and clopidogrel are used together after coronary, carotid, and intracranial stenting, and appear to be well tolerated. Evidence supporting clopidogrel also comes from cardiac trials, non-acute stroke/TIA trials, and most importantly, from an acute pilot trial of TIA and minor stroke, as reviewed below.
Cardiac Trials: The CURE trial of patients with acute coronary syndromes, also taking aspirin, found that clopidogrel 75 mg/day after a loading dose of 300 mg reduced the risk of stroke, myocardial infarction, and vascular death by 20% at 3-12 month follow-up, and the effect was apparent in the first 10 days.
Non-Acute Stroke/TIA Trials: The MATCH (Management of atherothrombosis with clopidogrel in high risk patients with recent TIA or ischemic stroke) trial was a secondary stroke prevention trial that enrolled 7599 patients, mostly in Europe.
Pilot Acute TIA/Stroke Trials: FASTER was a pilot trial based in Canada and run by collaborators who participated in the design of this trial.

Actual start date of recruitment	28 May 2010
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	Spain: 241
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Finland: 50
Country: Number of subjects enrolled	France: 98
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Australia: 104
Country: Number of subjects enrolled	Canada: 240
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	United States: 4043
Worldwide total number of subjects	4881
EEA total number of subjects	478

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)	2426
From 65 to 84 years	2455
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We enrolled patients in this randomized, double-blind, placebo-controlled trial from May 28, 2010, to December 19, 2017, at 269 sites in 10 countries in North America, Europe, Australia, and New Zealand, with the majority of the patients (82.8%) enrolled in the United States.

Pre-assignment

Screening details:

Patients who were at least 18 years of age were enrolled if they could undergo randomization within 12 hours after having an acute ischemic stroke with a score of 3 or less on the NIHSS or high-risk TIA with a score of 4 or more on the ABDC2 scale. They were also required to undergo head imaging to rule out intracranial bleeding or other conditions

Period 1

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

Blinding implementation details:

Medication bottles were coded with unique randomization numbers. The dataset linking the randomization number to the actual treatment (clopidogrel or placebo) was generated and maintained at the Neurological Emergencies Treatment Trials Network Statistical and Data Management Center. The electronic file that contained partially unblinded treatment assignment (e.g., A=clopidogrel, B=placebo) was only accessible to unblinded personnel when preparing unblinded (closed) reports for the DSMB.

Arms

Are arms mutually exclusive?	Yes
Arm title	clopidogrel/aspirin

Arm description:

Day 1: 8 tablets of clopidogrel 75 mg (loading dose of 600 mg)
From D2 to D90: one tablet of clopidogrel 75 mg and 50-325 mg of aspirin per day

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

Dosage and administration details:

Day 1: 8 tablets of clopidogrel 75 mg (loading dose of 600 mg)
From D2 to D90: one tablet of clopidogrel 75 mg

Investigational medicinal product name	open label aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Subjects will receive open label aspirin (50 mg – 325 mg), with dose at the discretion of the treating physician
From D2 to D90: 50-325 mg of aspirin per day

Arm title	placebo/aspirin

Arm description:

Day 1: 8 tablets of placebo 75 mg (loading dose of 600 mg)

From D2 to D90: one tablet of placebo 75 mg and 50-325 mg of aspirin per day

Arm type	Placebo
Investigational medicinal product name	open label aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Subjects will receive open label aspirin (50 mg – 325 mg), with dose at the discretion of the treating physician
From D2 to D90: 50-325 mg of aspirin per day

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: 8 tablets of placebo 75 mg (loading dose of 600 mg)
From D2 to D90: one tablet of placebo 75 mg

Number of subjects in period 1	clopidogrel/aspirin	placebo/aspirin
Started	2432	2449
Completed	2276	2281
Not completed	156	168
Consent withdrawn by subject	63	62
Lost to follow-up	93	106

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	4881	4881	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2426	2426	
From 65-84 years	2455	2455	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2195	2195	
Male	2686	2686	

Subject analysis sets

Subject analysis set title	as-treated analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

We performed a secondary, as-treated analysis of the primary outcome that included patients who had received at least one dose of a trial regimen, with data censored 1 day after permanent discontinuation of trial medication.

Reporting group values	as-treated analysis		
Number of subjects	4819		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)			
From 65-84 years			
85 years and over	0		

Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	clopidogrel/aspirin
Reporting group description:	
Day 1: 8 tablets of clopidogrel 75 mg (loading dose of 600 mg) From D2 to D90: one tablet of clopidogrel 75 mg and 50-325 mg of aspirin per day	
Reporting group title	placebo/aspirin
Reporting group description:	
Day 1: 8 tablets of placebo 75 mg (loading dose of 600 mg) From D2 to D90: one tablet of placebo 75 mg and 50-325 mg of aspirin per day	
Subject analysis set title	as-treated analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
We performed a secondary, as-treated analysis of the primary outcome that included patients who had received at least one dose of a trial regimen, with data censored 1 day after permanent discontinuation of trial medication.	

Primary: risk of a composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes (major ischemic events)

End point title	risk of a composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes (major ischemic events)
End point description:	
End point type	Primary
End point timeframe:	
90 days (with a window of ±14 days) after randomization	

End point values	clopidogrel/aspirin	placebo/aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2432	2449		
Units: number of patients	121	160		

Attachments (see zip file)	Table 2. Efficacy and Safety Outcomes/nejmoa1800410_t2.jpg Figure 2. Primary Efficacy and Safety

Statistical analyses

Statistical analysis title	composite primary efficacy outcome
Statistical analysis description:	
We determined that a sample of 4150 patients would provide the trial with a power of 90% to detect a hazard ratio of 0.75 with a two-sided alpha level of 0.05 on the basis of an event rate of 15% in the aspirin-only group. The sample was inflated to account for two interim analyses of the primary efficacy outcome with the use of an O'Brien–Fleming spending function.	
Comparison groups	clopidogrel/aspirin v placebo/aspirin

Number of subjects included in analysis	4881
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.94

Secondary: risk of ischemic stroke

End point title	risk of ischemic stroke

End point description:

End point type	Secondary

End point timeframe:

90 days (with a window of ±14 days) after randomization

End point values	clopidogrel/aspirin	placebo/aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2432	2449		
Units: number of patients	112	155		

Attachments (see zip file)	Table 2. Efficacy and Safety Outcomes/nejmoa1800410_t2.jpg

Statistical analyses

Statistical analysis title	secondary outcome of ischemic stroke
Comparison groups	clopidogrel/aspirin v placebo/aspirin
Number of subjects included in analysis	4881
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.92

Secondary: outcome of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage

End point title	outcome of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage

End point description:

End point type	Secondary

End point timeframe:

90 days (with a window of ±14 days) after randomization

End point values	clopidogrel/aspirin	placebo/aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2432	2449		
Units: number of patients	141	167		

Statistical analyses

Statistical analysis title	secondary outcome of combined events

Statistical analysis description:

outcome of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage

Comparison groups	clopidogrel/aspirin v placebo/aspirin
Number of subjects included in analysis	4881
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.05

Other pre-specified: primary safety outcome of major hemorrhage	
End point title	primary safety outcome of major hemorrhage
End point description:	
End point type	Other pre-specified
End point timeframe:	
90 days (with a window of ±14 days) after randomization	

End point values	clopidogrel/aspirin	placebo/aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2432	2449		
Units: number of patients	23	10		

Attachments (see zip file)	Table 2. Efficacy and Safety Outcomes/nejmoa1800410_t2.jpg Figure 2. Primary Efficacy and Safety

Statistical analyses

Statistical analysis title	primary safety outcome of major hemorrhage
Comparison groups	clopidogrel/aspirin v placebo/aspirin
Number of subjects included in analysis	4881
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	4.87

Other pre-specified: secondary safety outcome of minor hemorrhage	
End point title	secondary safety outcome of minor hemorrhage
End point description:	
End point type	Other pre-specified
End point timeframe:	
90 days (with a window of ±14 days) after randomization	

End point values	clopidogrel/aspirin	placebo/aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2432	2449		
Units: number of patients	40	13		

Statistical analyses

Statistical analysis title	Secondary safety outcome of minor hemorrhage
Comparison groups	clopidogrel/aspirin v placebo/aspirin
Number of subjects included in analysis	4881
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	5.85

Other pre-specified: major ischemic events

End point title	major ischemic events

End point description:

End point type	Other pre-specified

End point timeframe:

90 days (with a window of ±14 days) after randomization

End point values	clopidogrel/aspirin	placebo/aspirin	as-treated analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2398	2421	4819	
Units: number pf patients	102	141	243	

Statistical analyses

Statistical analysis title	as-treated major ischemic events
Comparison groups	placebo/aspirin v clopidogrel/aspirin
Number of subjects included in analysis	4819
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.94

Other pre-specified: as treated major hemorrhage	
End point title	as treated major hemorrhage
End point description:	
End point type	Other pre-specified
End point timeframe:	
Patients were followed for 90 days (with a window of +/- 14 days) after randomization.	

End point values	clopidogrel/aspirin	placebo/aspirin	as-treated analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2398	2421	4819	
Units: number of subjects	21	6	27	

Statistical analyses

Statistical analysis title	as-treated major hemorrhage
Comparison groups	clopidogrel/aspirin v placebo/aspirin
Number of subjects included in analysis	4819
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	3.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	8.85

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were followed for 90 days (with a window of +/- 14 days) after randomization.

Adverse event reporting additional description:

To reduce the risk of hemorrhage, subjects were monitored carefully. Study medications were stopped if bleeding or other major complications occurred and before any elective procedure. To mitigate potential risk of dipyridamole, use was prohibited. Non-serious AEs were not collected unless they qualified as a Clinical Outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Adverse Events

Reporting group description:

Serious Adverse Events and Clinical Outcomes classified as Adverse Event

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	764 / 4881 (15.65%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carcinoid tumour			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid body tumour			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to meninges			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pancreatic carcinoma				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Small intestine carcinoma				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Accelerated hypertension				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic aneurysm				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic dissection				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Aortic stenosis				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arterial occlusive disease				

subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	7 / 4881 (0.14%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	6 / 4881 (0.12%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	7 / 4881 (0.14%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	3 / 4881 (0.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral vascular disorder				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subclavian steal syndrome				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Arterial repair				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac pacemaker insertion				
subjects affected / exposed	3 / 4881 (0.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardioversion				

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stent insertion				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Carotid endarterectomy				
subjects affected / exposed	14 / 4881 (0.29%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary revascularisation				
subjects affected / exposed	6 / 4881 (0.12%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Drug rehabilitation				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endarterectomy				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-cerebral aneurysm operation				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrectomy				

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff repair				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toe amputation				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac death				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chest discomfort				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	15 / 4881 (0.31%)			
occurrences causally related to treatment / all	2 / 15			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Implant site haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasal cavity mass			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	7 / 4881 (0.14%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	6 / 4881 (0.12%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 3			
Respiratory failure				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Acute psychosis				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute stress disorder				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Confusional state				

subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Conversion disorder			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
dysthymic disorder			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	5 / 4881 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
somatisation disorder			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stress			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspiration bronchial			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheterisation cardiac			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin increased			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Craniocerebral injury			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	6 / 4881 (0.12%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple fractures			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Acute coronary syndrome			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Arrhythmia			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	39 / 4881 (0.80%)		
occurrences causally related to treatment / all	0 / 39		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Cardiac failure			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Cardiomyopathy acute			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congestive cardiomyopathy			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	5 / 4881 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Heart valve incompetence			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracardiac thrombus			
subjects affected / exposed	7 / 4881 (0.14%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	8 / 4881 (0.16%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 2			
Pericardial effusion				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Balance disorder				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery dissection				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				

subjects affected / exposed	27 / 4881 (0.55%)		
occurrences causally related to treatment / all	0 / 27		
deaths causally related to treatment / all	0 / 0		
Central nervous system lesion			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral venous thrombosis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	40 / 4881 (0.82%)		
occurrences causally related to treatment / all	0 / 42		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
complex partial seizures			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
complicated migraine			

subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
convulsion			
subjects affected / exposed	19 / 4881 (0.39%)		
occurrences causally related to treatment / all	0 / 20		
deaths causally related to treatment / all	0 / 0		
Diabetic hyperglycaemic coma			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolic stroke			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	5 / 4881 (0.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Guillain-Barre syndrome			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	6 / 4881 (0.12%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Haemorrhagic transformation stroke			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Headache			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intracranial haematoma			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			

subjects affected / exposed	195 / 4881 (4.00%)		
occurrences causally related to treatment / all	0 / 201		
deaths causally related to treatment / all	0 / 3		
Lacunar infarction			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	5 / 4881 (0.10%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	3 / 4881 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Neurological symptom			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Reversible ischaemic neurological deficit			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Speech disorder			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	6 / 4881 (0.12%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	10 / 4881 (0.20%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	104 / 4881 (2.13%)		
occurrences causally related to treatment / all	0 / 116		
deaths causally related to treatment / all	0 / 0		
Tremor			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	11 / 4881 (0.23%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Melaena			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 4881 (0.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Erythema			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pruritus			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

calculus ureteric			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
renal failure acute			
subjects affected / exposed	8 / 4881 (0.16%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Renal infarct			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Arthritis reactive			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Costochondritis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Cellulitis			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
lobar pneumonia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
meningitis lepto			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurosyphilis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal sepsis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	10 / 4881 (0.20%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 1		
Pneumonia influenzal			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
sepsis			
subjects affected / exposed	8 / 4881 (0.16%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Sinusitis			

subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	7 / 4881 (0.14%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 4881 (0.08%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 4881 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	4 / 4881 (0.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 4881 (3.54%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 4881 (0.16%)		
occurrences (all)	8		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	8 / 4881 (0.16%)		
occurrences (all)	8		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Myocardial infarction			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Nervous system disorders			
Cerebral amyloid angiopathy			

subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Cerebrovascular accident			
subjects affected / exposed	7 / 4881 (0.14%)		
occurrences (all)	7		
Haemorrhage intracranial			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences (all)	2		
Haemorrhagic transformation stroke			
subjects affected / exposed	6 / 4881 (0.12%)		
occurrences (all)	6		
Hypoaesthesia			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Ischaemic stroke			
subjects affected / exposed	32 / 4881 (0.66%)		
occurrences (all)	33		
Lacunar infarction			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Transient ischaemic attack			
subjects affected / exposed	82 / 4881 (1.68%)		
occurrences (all)	89		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences (all)	2		
Haematochezia			

subjects affected / exposed	4 / 4881 (0.08%)		
occurrences (all)	4		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	8 / 4881 (0.16%)		
occurrences (all)	8		
Haemoptysis			
subjects affected / exposed	1 / 4881 (0.02%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	2 / 4881 (0.04%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 4881 (0.08%)		
occurrences (all)	4		

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? Yes

Date	Interruption	Restart date
30 June 2014	POINT study drug shipments were temporarily suspended due to a delay in the delivery of new study drug from the manufacturer.	15 August 2014
01 June 2016	POINT study drug shipments were temporarily suspended due to a delay in the delivery of new study drug from the manufacturer.	01 November 2016
19 December 2017	Trial enrollment was halted due to confirmation of a significant excess in the number of patients with major hemorrhage in the combined antiplatelet group, and a planned analysis determined that a treatment effect had crossed the significance boundary for efficacy.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Patients with moderate-to-severe stroke, those with cardioembolic stoke, and those who are candidates for thrombolysis or thromobectomy were not represented int he trial, so results cannot be generalized to these groups.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29766750