# 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 |
| Scientific contact | Kelley Rosborough, Emmes, 1 3012511161, krosborough@emmes.com |

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<br>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<br>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<br>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<br>Units: Subjects | | | |
| Female<br>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)<br>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)<br>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<br>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<br>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 | | | |

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|---|---|---|---|---|
| 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 | | | | |

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|---|---|---|---|---|
| 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 | | | | |

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|---|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|---|
| 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 | | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|---|
| 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 | | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|---|
| 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 | | | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|---|
| 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