



Clinical trial results:

A Double-blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization

Summary

| | |
|--------------------------|---|
| EudraCT number | 2012-004208-37 |
| Trial protocol | IT NL BE SE CZ HU ES DE GR FI NO IE DK IS |
| Global end of trial date | 29 July 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 04 August 2017 |
| First version publication date | 04 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20120153 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01813422 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 | 29 July 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study evaluated whether low-density lipoprotein (LDL-C) lowering with evolocumab (AMG 145) resulted in greater change from baseline in percent atheroma volume (PAV) at week 78 than placebo in adults with coronary artery disease taking lipid lowering therapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 18 April 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 59 |
| Country: Number of subjects enrolled | United States: 115 |
| Country: Number of subjects enrolled | Belgium: 28 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Hungary: 145 |
| Country: Number of subjects enrolled | Iceland: 7 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Italy: 29 |
| Country: Number of subjects enrolled | Netherlands: 148 |
| Country: Number of subjects enrolled | Norway: 14 |
| Country: Number of subjects enrolled | Poland: 95 |
| Country: Number of subjects enrolled | Russian Federation: 69 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Spain: 38 |
| Country: Number of subjects enrolled | Sweden: 15 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Argentina: 13 |
| Country: Number of subjects enrolled | Brazil: 4 |
| Country: Number of subjects enrolled | Chile: 8 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Australia: 34 |
| Country: Number of subjects enrolled | Korea, Republic of: 9 |
| Country: Number of subjects enrolled | Malaysia: 10 |
| Country: Number of subjects enrolled | Singapore: 1 |
| Country: Number of subjects enrolled | South Africa: 45 |
| Country: Number of subjects enrolled | Taiwan: 2 |
| Worldwide total number of subjects | 970 |
| EEA total number of subjects | 590 |

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) | 661 |
| From 65 to 84 years | 308 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 163 centers in 30 countries in Europe, North America, Asia Pacific, and Latin America. The first participant was enrolled on 18 April 2013 and the last participant enrolled on 12 January 2015.

Pre-assignment

Screening details:

Participants who met all entry criteria were randomized 1:1 to receive evolocumab 420 mg once monthly (QM) subcutaneous (SC) or placebo QM SC for 76 weeks. Randomization was stratified by region.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered by subcutaneous injection once a month

| | |
|------------------|------------|
| Arm title | Evolocumab |
|------------------|------------|

Arm description:

Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Evolocumab |
| Investigational medicinal product code | AMG 145 |
| Other name | Repatha |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Evolocumab 420 mg administered by subcutaneous injection once a month

| Number of subjects in period 1 | Placebo | Evolocumab |
|---------------------------------------|---------|------------|
| Started | 486 | 484 |
| Received Treatment | 484 | 484 |
| Completed | 466 | 468 |
| Not completed | 20 | 16 |
| Adverse event, serious fatal | 2 | 3 |
| Consent withdrawn by subject | 14 | 8 |
| Sponsor Decision | 2 | 1 |
| Lost to follow-up | 2 | 4 |

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks. | |
| Reporting group title | Evolocumab |
| Reporting group description: | |
| Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks. | |

| Reporting group values | Placebo | Evolocumab | Total |
|---|---------|------------|-------|
| Number of subjects | 486 | 484 | 970 |
| Age categorical Units: Subjects | | | |
| Age Continuous Units: years | | | |
| arithmetic mean | 59.8 | 59.8 | |
| standard deviation | ± 8.8 | ± 9.6 | - |
| Gender, Male/Female Units: Subjects | | | |
| Female | 135 | 135 | 270 |
| Male | 351 | 349 | 700 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 0 | 2 |
| Asian | 17 | 14 | 31 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 5 | 4 | 9 |
| White | 453 | 456 | 909 |
| Multiple | 6 | 7 | 13 |
| Other | 3 | 2 | 5 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 24 | 34 | 58 |
| Not Hispanic or Latino | 462 | 450 | 912 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Stratification Factor: Geographical Region Units: Subjects | | | |
| North America | 88 | 86 | 174 |
| Europe | 332 | 332 | 664 |
| Latin America | 16 | 15 | 31 |
| Asia Pacific | 50 | 51 | 101 |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks. | |
| Reporting group title | Evolocumab |
| Reporting group description: | |
| Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks. | |

Primary: Change from Baseline in Percent Atheroma Volume at Week 78

| | |
|---|--|
| End point title | Change from Baseline in Percent Atheroma Volume at Week 78 |
| End point description: | |
| Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. The extent of atherosclerosis was expressed as percent atheroma volume (PAV) in a ≥ 40 mm segment of one targeted (imaged) coronary artery, calculated as the percentage of the total vessel volume occupied by atheroma. This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set). | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and week 78 | |

| End point values | Placebo | Evolocumab | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 423 | | |
| Units: percent atheroma volume | | | | |
| least squares mean (standard error) | 0.053 (\pm 0.189) | -0.955 (\pm 0.19) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Primary Analysis of Change from Baseline in PAV |
| Comparison groups | Placebo v Evolocumab |
| Number of subjects included in analysis | 846 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -1.007 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.375 |
| upper limit | -0.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.187 |

Notes:

[1] - ANCOVA model included terms for the treatment group, the geographic region stratification factor, and baseline PAV.

Secondary: Change from Baseline in Total Atheroma Volume at Week 78

| | |
|-----------------|--|
| End point title | Change from Baseline in Total Atheroma Volume at Week 78 |
|-----------------|--|

End point description:

Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. Total atheroma volume (TAV) in a ≥ 40 mm segment of the targeted coronary artery was calculated as the average plaque area over the number of images that were evaluated by IVUS multiplied by the median vessel length to compensate for differences in segment length between participants.

This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set).

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

End point timeframe:

Baseline and week 78

| End point values | Placebo | Evolocumab | | |
|-------------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 423 | | |
| Units: mm ³ | | | | |
| least squares mean (standard error) | -0.91 (\pm 1.214) | -5.799 (\pm 1.216) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Analysis of Change from Baseline in TAV |
| Comparison groups | Placebo v Evolocumab |
| Number of subjects included in analysis | 846 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -4.889 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.247 |
| upper limit | -2.531 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.201 |

Notes:

[2] - ANCOVA model included terms for the treatment group, the geographic region stratification factor, and baseline TAV.

Secondary: Percentage of Participants with Regression in Percent Atheroma Volume

| | |
|-----------------|---|
| End point title | Percentage of Participants with Regression in Percent Atheroma Volume |
|-----------------|---|

End point description:

Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. The extent of atherosclerosis was expressed as percent atheroma volume (PAV) in a ≥ 40 mm segment of one targeted (imaged) coronary artery, calculated as the percentage of the total vessel volume occupied by atheroma. Regression in PAV was defined as any reduction from baseline in PAV.

This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set)

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

End point timeframe:

Baseline and week 78

| End point values | Placebo | Evolocumab | | |
|-----------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 423 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 47.3 (42.6 to 52) | 64.3 (59.6 to 68.7) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Analysis of Regression in PAV |
| Comparison groups | Placebo v Evolocumab |
| Number of subjects included in analysis | 846 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.3 |
| upper limit | 23.5 |

Notes:

[3] - Based on CMH test stratified by geographic region.

Secondary: Percentage of Participants with Regression in Total Atheroma Volume

| | |
|--|---|
| End point title | Percentage of Participants with Regression in Total Atheroma Volume |
| End point description: | |
| <p>Intravascular ultrasound (IVUS) was used to visualize the extent of atherosclerotic plaques in the coronary artery lumen. Total atheroma volume (TAV) in a ≥ 40 mm segment of the targeted coronary artery was calculated as the average plaque area over the number of images that were evaluated by IVUS multiplied by the median vessel length to compensate for differences in segment length between participants. Regression in TAV was defined as any reduction from baseline in TAV.</p> <p>This endpoint was analyzed in randomized participants who received at least 1 dose of study drug, with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS analysis set).</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 78 | |

| End point values | Placebo | Evolocumab | | |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 423 | 423 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 48.9 (44.2 to 53.7) | 61.5 (56.7 to 66) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Analysis of Regression in TAV |
| Comparison groups | Placebo v Evolocumab |
| Number of subjects included in analysis | 846 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 12.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.8 |
| upper limit | 19.1 |

Notes:

[4] - Based on CMH test stratified by geographic region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until week 80

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Participants received placebo to evolocumab administered by subcutaneous injection once a month for 76 weeks.

| | |
|-----------------------|------------|
| Reporting group title | Evolocumab |
|-----------------------|------------|

Reporting group description:

Participants received 420 mg evolocumab administered by subcutaneous injection once a month for 76 weeks.

| Serious adverse events | Placebo | Evolocumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 142 / 484 (29.34%) | 135 / 484 (27.89%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acoustic neuroma | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basosquamous carcinoma of skin | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign pancreatic neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer stage I, with cancer in situ | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervix carcinoma stage 0 | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chemodectoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal tract adenoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung adenocarcinoma metastatic | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung carcinoma cell type unspecified stage III | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin cancer | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteral neoplasm | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 484 (0.83%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasoconstriction | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vessel perforation | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary revascularisation | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mammoplasty | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 6 / 484 (1.24%) | 11 / 484 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Puncture site haemorrhage | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent restenosis | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vessel puncture site haemorrhage | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical polyp | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 4 / 484 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paranoia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriogram coronary | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb traumatic amputation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural dizziness | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skeletal injury | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 3 / 484 (0.62%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 5 / 484 (1.03%) | 6 / 484 (1.24%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 11 / 484 (2.27%) | 17 / 484 (3.51%) | |
| occurrences causally related to treatment / all | 0 / 12 | 2 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 7 / 484 (1.45%) | 8 / 484 (1.65%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 5 / 484 (1.03%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 4 / 484 (0.83%) | 6 / 484 (1.24%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 13 / 484 (2.69%) | 7 / 484 (1.45%) | |
| occurrences causally related to treatment / all | 0 / 13 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery dissection | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 5 / 484 (1.03%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 484 (0.83%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 3 / 484 (0.62%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinoatrial block | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial palsy | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial aneurysm | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cataract | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic retinopathy | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinopathy | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileal perforation | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder enlargement | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Bladder prolapse | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 3 / 484 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 484 (0.41%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 484 (0.62%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Costochondritis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 4 / 484 (0.83%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylitis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebral foraminal stenosis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain abscess | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective staphylococcal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye infection toxoplasmal | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 484 (1.03%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyonephrosis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 484 (0.41%) | 2 / 484 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 484 (0.00%) | 1 / 484 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obesity | | | |
| subjects affected / exposed | 1 / 484 (0.21%) | 0 / 484 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | Evolocumab | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 120 / 484 (24.79%) | 114 / 484 (23.55%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 34 / 484 (7.02%) | 29 / 484 (5.99%) | |
| occurrences (all) | 36 | 32 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 32 / 484 (6.61%) | 21 / 484 (4.34%) | |
| occurrences (all) | 37 | 24 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 29 / 484 (5.99%) | 19 / 484 (3.93%) | |
| occurrences (all) | 34 | 21 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 26 / 484 (5.37%) | 33 / 484 (6.82%) | |
| occurrences (all) | 31 | 35 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| Myalgia | | | |
| subjects affected / exposed | 27 / 484 (5.58%) | 34 / 484 (7.02%) | |
| occurrences (all) | 31 | 39 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 30 April 2013 | Major changes included: <ul style="list-style-type: none">•added known hemorrhagic stroke and personal or family history of hereditary muscular disorders to exclusion criteria•added clarification to the criteria for the target coronary artery for IVUS•added an alert threshold for elevated triglycerides•updated the criteria for withholding investigational product to include criteria for withholding atorvastatin•updated the serious adverse event reporting window•updated the prohibited treatments section•implemented minor clarifications and error corrections |
| 20 December 2013 | Major changes included: <ul style="list-style-type: none">•modified inclusion criteria to allow additional statins beyond atorvastatin (simvastatin, rosuvastatin, pravastatin, lovastatin, and pitastatin); statin intolerant subjects (limit up to 10%); niacin and ezetimibe background therapy, provided it was stable for 4 weeks prior to screening•added inclusion criteria that subjects had be on a stable, optimized background therapy and on an effective statin dose of at least atorvastatin 20mg daily or equivalent•added exclusion of subjects on mipomersen or lomitapide in the last 12 months prior to LDL-C screening•clarified definition of regression by PAV and TAV for secondary endpoints•updated safety sections per the new Amgen template•changed dosing nomenclature from Q4W to QM•added device language to allow subjects to use the 3.5 mL personal injector when available•implemented other clarifications to inclusion/exclusion criteria |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported