

**Clinical trial results:****A Randomized, Double-blind, Double-dummy, Active-controlled, Parallel-group, Multicenter Study to Compare the Safety of Rivaroxaban versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Subjects with Acute Coronary Syndrome****Summary**

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2014-004266-26             |
| Trial protocol           | BE SE CZ NL HU ES IT BG DK |
| Global end of trial date | 14 October 2016            |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 27 October 2017 |
| First version publication date | 27 October 2017 |

**Trial information****Trial identification**

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | RIVAROXACS2002 |
|-----------------------|----------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02293395 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Janssen Research & Development, LLC  |
| Sponsor organisation address | 920 Highway 202 S, Raritan, NJ, United States, 08869                                       |
| Public contact               | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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                       | 14 October 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 October 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to estimate the bleeding risk with rivaroxaban, compared with acetyl salicylic acid (ASA), in addition to a single antiplatelet P2Y12 inhibitor agent (clopidogrel or ticagrelor), in subjects with a recent acute coronary syndrome (ACS) (including ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation acute coronary syndrome [NSTE-ACS]).

Protection of trial subjects:

The safety evaluations included bleeding events, other adverse events, and clinical laboratory tests (hematology and clinical chemistry) that were relevant and clinically meaningful to a serious adverse event (SAE) or endpoint event. Safety data obtained during the study were reviewed on a routine basis by an unblinded, independent data monitoring committee (IDMC). This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 22 April 2015 |
| 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 | Argentina: 131          |
| Country: Number of subjects enrolled | Australia: 35           |
| Country: Number of subjects enrolled | Belgium: 89             |
| Country: Number of subjects enrolled | Bulgaria: 161           |
| Country: Number of subjects enrolled | Brazil: 162             |
| Country: Number of subjects enrolled | Canada: 84              |
| Country: Number of subjects enrolled | Czech Republic: 71      |
| Country: Number of subjects enrolled | Denmark: 3              |
| Country: Number of subjects enrolled | Spain: 122              |
| Country: Number of subjects enrolled | France: 57              |
| Country: Number of subjects enrolled | Hungary: 201            |
| Country: Number of subjects enrolled | Italy: 134              |
| Country: Number of subjects enrolled | Japan: 59               |
| Country: Number of subjects enrolled | Korea, Republic of: 54  |
| Country: Number of subjects enrolled | Netherlands: 134        |
| Country: Number of subjects enrolled | Poland: 333             |
| Country: Number of subjects enrolled | Russian Federation: 481 |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Sweden: 79         |
| Country: Number of subjects enrolled | Turkey: 200        |
| Country: Number of subjects enrolled | Ukraine: 266       |
| Country: Number of subjects enrolled | United States: 181 |
| Worldwide total number of subjects   | 3037               |
| EEA total number of subjects         | 1384               |

Notes:

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**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)                      | 1776 |
| From 65 to 84 years                       | 1250 |
| 85 years and over                         | 11   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 3,145 subjects were screened for eligibility, of these 108 subjects were screening failures and the remaining 3,037 subjects were randomized.

### 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                | Investigator, Subject          |

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | Rivaroxaban 2.5 mg Twice Daily (BID) |

Arm description:

Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Rivaroxaban  |
| Investigational medicinal product code | BAY59-7939   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received oral dose of 2.5 mg rivaroxaban BID for a minimum of 180 days, and up to 360 days of treatment.

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

Dosage and administration details:

Subjects received oral dose of placebo matching to 100 mg ASA OD along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Acetylsalicylic acid 100 mg Once Daily (OD) |
|------------------|---|

Arm description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

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

Dosage and administration details:

Subjects received oral dose of placebo matching to 2.5 mg rivaroxaban BID along with either clopidogrel

75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|  |                      |
|--|----------------------|
| Investigational medicinal product name | Acetylsalicylic acid |
| Investigational medicinal product code |                      |
| Other name                             | Aspirin              |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Subjects received oral dose of 100 mg ASA OD for a minimum of 180 days, and up to 360 days of treatment.

| Number of subjects in period 1 | Rivaroxaban 2.5 mg<br>Twice Daily (BID) | Acetylsalicylic acid<br>100 mg Once Daily<br>(OD) |
|--------------------------------|---|---|
|                                |   |   |
| Started                        | 1519                                    | 1518  |
| Treated                        | 1510                                    | 1506 <sup>[1]</sup>                               |
| Completed                      | 1510                                    | 1511  |
| Not completed                  | 9                                       | 7   |
| Consent withdrawn by subject   | 8                                       | 7   |
| Lost to follow-up              | 1                                       | -   |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: To provide more clarification for the subjects who were treated and to justify safety analysis population, we have created a milestone in subject disposition as "Treated".

## Baseline characteristics

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Rivaroxaban 2.5 mg Twice Daily (BID) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|                       |   |
|-----------------------|---|
| Reporting group title | Acetylsalicylic acid 100 mg Once Daily (OD) |
|-----------------------|---|

Reporting group description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

| Reporting group values                      | Rivaroxaban 2.5 mg Twice Daily (BID) | Acetylsalicylic acid 100 mg Once Daily (OD) | Total |
|---|--------------------------------------|---|-------|
| Number of subjects                          | 1519                                 | 1518  | 3037  |
| Title for AgeCategorical<br>Units: subjects |                                      |   |       |
| Children (2-11 years)                       | 0                                    | 0   | 0     |
| Adolescents (12-17 years)                   | 0                                    | 0   | 0     |
| Adults (18-64 years)                        | 887                                  | 889   | 1776  |
| From 65 to 84 years                         | 627                                  | 623   | 1250  |
| 85 years and over                           | 5                                    | 6   | 11    |
| Title for AgeContinuous<br>Units: years     |                                      |   |       |
| arithmetic mean                             | 62.7                                 | 62.9  |       |
| standard deviation                          | ± 9.14                               | ± 8.82                                      | -     |
| Title for Gender<br>Units: subjects         |                                      |   |       |
| Female                                      | 385                                  | 377   | 762   |
| Male  | 1134                                 | 1141  | 2275  |

## End points

### End points reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Rivaroxaban 2.5 mg Twice Daily (BID) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received oral dose of 2.5 milligram (mg) rivaroxaban BID and Acetylsalicylic acid (ASA) placebo once daily (OD) along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|                       |   |
|-----------------------|---|
| Reporting group title | Acetylsalicylic acid 100 mg Once Daily (OD) |
|-----------------------|---|

Reporting group description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

### Primary: Number of Subjects with non Coronary Artery Bypass Graft-Related (non CABG-related) Thrombolysis in Myocardial Infarction (TIMI) Clinically Significant Bleeding Events

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with non Coronary Artery Bypass Graft-Related (non CABG-related) Thrombolysis in Myocardial Infarction (TIMI) Clinically Significant Bleeding Events |
|-----------------|---|

End point description:

Non CABG-related TIMI clinically significant bleeding events are sum of non CABG-related TIMI major bleeding events, TIMI minor bleeding events and TIMI bleeding events requiring medical attention. Major: any symptomatic intracranial bleeding: clinically overt signs of hemorrhage with hemoglobin (Hb) drop of greater than or equal to ( $\geq$ )5 gram per deciliter (g/dl) (or absolute drop in hematocrit of  $\geq$ 15%) and fatal bleeding (results in death within 7 days); Minor: clinically overt sign of hemorrhage with Hb drop of 3 - <5 g/dl (or drop in hematocrit of 9 - <15%); requiring medical attention: bleeding event that required medical, surgical treatment/laboratory evaluation and did not meet criteria for major/minor bleeding event. Population analyzed included all randomized subjects who had received at least one dose of study drug and had events between randomization and last dose of study drug +2 days or untreated subjects who had events between randomization to 2 days thereafter.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment until follow-up (up to 390 days)

| End point values            | Rivaroxaban 2.5 mg Twice Daily (BID) | Acetylsalicylic acid 100 mg Once Daily (OD) |  |  |
|-----------------------------|--------------------------------------|---|--|--|
| Subject group type          | Reporting group                      | Reporting group                             |  |  |
| Number of subjects analysed | 1519                                 | 1518  |  |  |
| Units: subjects             | 80                                   | 74  |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Non CABG-related TIMI  |
| Comparison groups          | Rivaroxaban 2.5 mg Twice Daily (BID) v Acetylsalicylic acid 100 mg Once Daily (OD) |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 3037              |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | other             |
| P-value                                 | = 0.584           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.09              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.8               |
| upper limit                             | 1.5               |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 390 days

Adverse event reporting additional description:

Population analyzed included all randomized subjects who had received at least one dose of study drug and had events between randomization and last dose of study drug +2 days.

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

### Dictionary used

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

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

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Acetylsalicylic acid 100 mg Once Daily (OD) |
|-----------------------|---|

Reporting group description:

Subjects received oral dose of 100 mg ASA OD and rivaroxaban placebo BID along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Rivaroxaban 2.5 mg Twice Daily (BID) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received oral dose of 2.5 mg rivaroxaban BID and ASA placebo OD along with either clopidogrel 75 mg OD or ticagrelor 90 mg BID for a minimum of 180 days, and up to 360 days of treatment.

| <b>Serious adverse events</b>                                       | Acetylsalicylic acid<br>100 mg Once Daily<br>(OD) | Rivaroxaban 2.5 mg<br>Twice Daily (BID) |  |
|---|---|---|--|
| Total subjects affected by serious adverse events                   |   |   |  |
| subjects affected / exposed   | 138 / 1506 (9.16%)                                | 125 / 1510 (8.28%)                      |  |
| number of deaths (all causes)                                       | 9   | 7                                       |  |
| number of deaths resulting from adverse events                      |   |   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |  |
| Brain Neoplasm  |   |   |  |
| subjects affected / exposed   | 1 / 1506 (0.07%)                                  | 0 / 1510 (0.00%)                        |  |
| occurrences causally related to treatment / all                     | 0 / 1   | 0 / 0                                   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                                   |  |
| Cervix Carcinoma Recurrent  |   |   |  |
| subjects affected / exposed   | 1 / 1506 (0.07%)                                  | 0 / 1510 (0.00%)                        |  |
| occurrences causally related to treatment / all                     | 0 / 1   | 0 / 0                                   |  |
| deaths causally related to treatment / all                          | 0 / 1   | 0 / 0                                   |  |
| Colon Cancer Recurrent  |   |   |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Gastric Cancer</b>                           |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Gastrointestinal Carcinoma</b>               |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Hepatocellular Carcinoma</b>                 |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Laryngeal Cancer</b>                         |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Lung Neoplasm Malignant</b>                  |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pancreatic Carcinoma</b>                     |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |
| <b>Prostate Cancer</b>                          |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 2 / 1510 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Rectal Adenocarcinoma</b>                    |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>Renal Neoplasm</b>                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Salivary Gland Cancer Recurrent</b>          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Squamous Cell Carcinoma</b>                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Uterine Cancer</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Uterine Leiomyoma</b>                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vascular Neoplasm</b>                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vascular disorders</b>                       |                  |                  |  |
| <b>Aortic Aneurysm</b>                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Arteriosclerosis</b>                         |                  |                  |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Brachiocephalic Arteriosclerosis</b>         |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Hypertension</b>                             |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Hypertensive Crisis</b>                      |                  |                  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 5 / 1510 (0.33%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Hypotension</b>                              |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Peripheral Arterial Occlusive Disease</b>    |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Peripheral Artery Aneurysm</b>               |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Peripheral Artery Occlusion</b>              |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Peripheral Artery Stenosis</b>               |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                                 | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Subclavian Artery Stenosis</b>                           |                  |                  |  |
| subjects affected / exposed                                 | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Vascular Occlusion</b>                                   |                  |                  |  |
| subjects affected / exposed                                 | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all             | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Surgical and medical procedures</b>                      |                  |                  |  |
| <b>Inguinal Hernia Repair</b>                               |                  |                  |  |
| subjects affected / exposed                                 | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Lung Neoplasm Surgery</b>                                |                  |                  |  |
| subjects affected / exposed                                 | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Lymphadenectomy</b>                                      |                  |                  |  |
| subjects affected / exposed                                 | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>General disorders and administration site conditions</b> |                  |                  |  |
| <b>Chest Pain</b>   |                  |                  |  |
| subjects affected / exposed                                 | 2 / 1506 (0.13%) | 2 / 1510 (0.13%) |  |
| occurrences causally related to treatment / all             | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all                  | 0 / 0            | 0 / 0            |  |
| <b>Death</b>  |                  |                  |  |
| subjects affected / exposed                                 | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                  | 0 / 1            | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Implant Site Ulcer                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple Organ Dysfunction Syndrome             |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Non-Cardiac Chest Pain                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stent-Graft Endoleak                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular Stent Restenosis                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular Stent Stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Benign Prostatic Hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute Pulmonary Oedema                          |                  |                  |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Acute Respiratory Failure</b>                |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |
| <b>Asthma</b>                                   |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Chronic Obstructive Pulmonary Disease</b>    |                  |                  |
| subjects affected / exposed                     | 3 / 1506 (0.20%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Cough</b>                                    |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Dyspnoea</b>                                 |                  |                  |
| subjects affected / exposed                     | 4 / 1506 (0.27%) | 4 / 1510 (0.26%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pleurisy</b>                                 |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pulmonary Embolism</b>                       |                  |                  |
| subjects affected / exposed                     | 4 / 1506 (0.27%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pulmonary Mass</b>                           |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Pulmonary Oedema</b>                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 1506 (0.20%) | 3 / 1510 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Respiratory Failure</b>                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Psychiatric disorders</b>                    |                  |                  |  |
| <b>Alcohol Withdrawal Syndrome</b>              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Depression</b>                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Panic Attack</b>                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Investigations</b>                           |                  |                  |  |
| <b>Cardiac Stress Test Abnormal</b>             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Haemoglobin Decreased</b>                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Hepatic Enzyme Increased</b>                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver Function Test Increased                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mediastinoscopy                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight Decreased                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Alcohol Poisoning                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary Artery Restenosis                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 1506 (0.20%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand Fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heat Illness                                    |                  |                  |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Hip Fracture                                    |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Humerus Fracture                                |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Joint Dislocation                               |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Laceration                                      |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Ligament Sprain                                 |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Lower Limb Fracture                             |                  |                  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Lumbar Vertebral Fracture                       |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Radius Fracture                                 |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Spinal Fracture</b>                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Ulna Fracture</b>                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vascular Access Site Pain</b>                |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vascular Graft Occlusion</b>                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vascular Pseudoaneurysm</b>                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cardiac disorders</b>                        |                  |                  |  |
| <b>Acute Left Ventricular Failure</b>           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 3 / 1510 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Acute Myocardial Infarction</b>              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Angina Pectoris</b>                          |                  |                  |  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Angina Unstable</b>                          |                  |                  |
| subjects affected / exposed                     | 5 / 1506 (0.33%) | 5 / 1510 (0.33%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Aortic Valve Stenosis</b>                    |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Atrial Fibrillation</b>                      |                  |                  |
| subjects affected / exposed                     | 7 / 1506 (0.46%) | 3 / 1510 (0.20%) |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |
| <b>Atrial Flutter</b>                           |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Atrioventricular Block Second Degree</b>     |                  |                  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Bradycardia</b>                              |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Cardiac Failure</b>                          |                  |                  |
| subjects affected / exposed                     | 7 / 1506 (0.46%) | 9 / 1510 (0.60%) |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 11           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Cardiac Failure Acute</b>                    |                  |                  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac Failure Chronic                         |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 3 / 1510 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac Failure Congestive                      |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 2 / 1510 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiac Ventricular Thrombosis                  |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Cardiovascular Insufficiency                    |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Coronary Artery Disease                         |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 2 / 1510 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Coronary Artery Stenosis                        |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Intracardiac Thrombus                           |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| Mitral Valve Incompetence                       |                  |                  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Myocardial Fibrosis</b>                      |                  |                  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Myocardial Ischaemia</b>                     |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Myocardial Rupture</b>                       |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |
| <b>Pericarditis</b>                             |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pleuropericarditis</b>                       |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Postinfarction Angina</b>                    |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Sinus Arrest</b>                             |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Ventricular Extrasystoles</b>                |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Nervous system disorders</b>                 |                  |                  |  |
| <b>Carotid Artery Stenosis</b>                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Facial Paralysis</b>                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Intracranial Aneurysm</b>                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Presyncope</b>                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Seizure</b>                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Syncope</b>                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 1506 (0.20%) | 2 / 1510 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Vertebral Artery Stenosis</b>                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Blood and lymphatic system disorders</b>     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Anaemia   |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Vertigo   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo Positional                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Cataract  |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal Pain                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic Gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis Ulcerative                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum Intestinal                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Erosive Oesophagitis</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Gastritis</b>                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Gastroduodenitis</b>                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Intestinal Obstruction</b>                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Pancreatic Necrosis</b>                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| <b>Pancreatitis Acute</b>                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Pancreatitis Chronic</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Hepatobiliary disorders</b>                  |                  |                  |  |
| Cholangitis                                     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cholecystitis</b>                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 2 / 1510 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cholecystitis Acute</b>                      |                  |                  |  |
| subjects affected / exposed                     | 5 / 1506 (0.33%) | 3 / 1510 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cholelithiasis</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 3 / 1510 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Drug-Induced Liver Injury</b>                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Renal and urinary disorders</b>              |                  |                  |  |
| <b>Acute Kidney Injury</b>                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>Nephrolithiasis</b>                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Nephropathy Toxic</b>                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Renal Artery Stenosis</b>                    |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                            | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Renal Colic</b>                                     |                  |                  |  |
| subjects affected / exposed                            | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Ureterolithiasis</b>                                |                  |                  |  |
| subjects affected / exposed                            | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Urinary Retention</b>                               |                  |                  |  |
| subjects affected / exposed                            | 0 / 1506 (0.00%) | 2 / 1510 (0.13%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Urinary Tract Obstruction</b>                       |                  |                  |  |
| subjects affected / exposed                            | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                  |                  |  |
| <b>Costochondritis</b>                                 |                  |                  |  |
| subjects affected / exposed                            | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Intervertebral Disc Disorder</b>                    |                  |                  |  |
| subjects affected / exposed                            | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Intervertebral Disc Protrusion</b>                  |                  |                  |  |
| subjects affected / exposed                            | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| <b>Ligamentitis</b>                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Musculoskeletal Discomfort</b>               |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Osteoarthritis</b>                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Rapidly Progressive Osteoarthritis</b>       |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Rhabdomyolysis</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Rheumatoid Arthritis</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Tenosynovitis</b>                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Infections and infestations</b>              |                  |                  |  |
| <b>Appendicitis</b>                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Bronchitis</b>                               |                  |                  |  |

|  |                  |                  |
|--|------------------|------------------|
| subjects affected / exposed  | 1 / 1506 (0.07%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Diverticulitis</b>  |                  |                  |
| subjects affected / exposed  | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all                      | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Gangrene</b>  |                  |                  |
| subjects affected / exposed  | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Gastrointestinal Infection</b>                                    |                  |                  |
| subjects affected / exposed  | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all                      | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 1            |
| <b>H1n1 Influenza</b>  |                  |                  |
| subjects affected / exposed  | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                           | 0 / 1            | 0 / 0            |
| <b>Herpes Zoster</b>   |                  |                  |
| subjects affected / exposed  | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Infectious Pleural Effusion</b>                                   |                  |                  |
| subjects affected / exposed  | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Infective Exacerbation of Chronic Obstructive Airways Disease</b> |                  |                  |
| subjects affected / exposed  | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all                      | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all                           | 0 / 0            | 0 / 0            |
| <b>Influenza</b>   |                  |                  |

|   |                  |                  |
|---|------------------|------------------|
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 2 / 1510 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Orchitis</b>                                 |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Periodontitis</b>                            |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pneumonia</b>                                |                  |                  |
| subjects affected / exposed                     | 5 / 1506 (0.33%) | 7 / 1510 (0.46%) |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 7            |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |
| <b>Postoperative Wound Infection</b>            |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Pyelonephritis Chronic</b>                   |                  |                  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 2 / 1510 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Respiratory Tract Infection</b>              |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Spinal Cord Infection</b>                    |                  |                  |
| subjects affected / exposed                     | 0 / 1506 (0.00%) | 1 / 1510 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |
| <b>Urinary Tract Infection</b>                  |                  |                  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Metabolism and nutrition disorders</b>       |                  |                  |  |
| <b>Diabetes Mellitus</b>                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 1506 (0.13%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Hyperglycaemia</b>                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Hypoglycaemia</b>                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 1506 (0.07%) | 0 / 1510 (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: 1 %

| <b>Non-serious adverse events</b>                            | Acetylsalicylic acid<br>100 mg Once Daily<br>(OD) | Rivaroxaban 2.5 mg<br>Twice Daily (BID) |  |
|--|---|---|--|
| <b>Total subjects affected by non-serious adverse events</b> |   |   |  |
| subjects affected / exposed                                  | 84 / 1506 (5.58%)                                 | 81 / 1510 (5.36%)                       |  |
| <b>Vascular disorders</b>                                    |   |   |  |
| <b>Hypertension</b>  |   |   |  |
| subjects affected / exposed                                  | 22 / 1506 (1.46%)                                 | 23 / 1510 (1.52%)                       |  |
| occurrences (all)  | 24  | 24                                      |  |
| <b>General disorders and administration site conditions</b>  |   |   |  |
| <b>Chest Pain</b>  |   |   |  |
| subjects affected / exposed                                  | 19 / 1506 (1.26%)                                 | 11 / 1510 (0.73%)                       |  |
| occurrences (all)  | 21  | 11                                      |  |
| <b>Respiratory, thoracic and mediastinal disorders</b>       |   |   |  |
| <b>Cough</b>   |   |   |  |
| subjects affected / exposed                                  | 14 / 1506 (0.93%)                                 | 16 / 1510 (1.06%)                       |  |
| occurrences (all)  | 14  | 16                                      |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Dyspnoea                    |                   |                   |  |
| subjects affected / exposed | 39 / 1506 (2.59%) | 33 / 1510 (2.19%) |  |
| occurrences (all)           | 39                | 34                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 16 December 2014 | The following changes were made in this amendment: modified a number of the inclusion criteria to simplify enrollment of subjects into the study; changes were made to clarify: the definition of the primary endpoint as it related to TIMI clinically significant bleeding events, stratification, the composition and conduct of the committees, the data to be used in the analyses, and the planned interim analysis; changes were made to ensure the evaluation of the cytochrome P450 2C19 genotype in all subjects regardless of P2Y12 inhibitor choice and to modify the timing of parenteral anticoagulants during the index hospitalization to the first dose of the study agent for consistency with the guidelines and previous studies conducted in the acute coronary syndrome (ACS) population.   |
| 21 April 2015    | The following changes were made in this amendment: eligibility criteria was revised and it allowed for the inclusion of subjects with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) with positive biomarkers of myocardial necrosis without transient electrocardiogram (ECG) changes if there was a culprit lesion on coronary angiography demonstrating that a recent, active intracoronary atherothrombosis was identified; additionally, subjects with unstable angina without elevated cardiac biomarkers were eligible for enrollment based on ECG changes, a revascularization procedure, or an elevated TIMI risk score; furthermore, the adverse event reporting section was updated to exclude events that were suggestive of and reported as endpoint events from serious adverse event reporting and unblinding procedures. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Study population was homogenous with limited participation of non-Caucasian subjects. Randomization was not performed for use of P2Y12 inhibitor; strata comparisons between bleeding and efficacy endpoints are confounded and were not planned.

Notes: