

**Clinical trial results:**

**A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO EVALUATE THE EFFECT OF 300 MG OF INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR ASCVD-RISK EQUIVALENTS AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)**

**Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-001846-90 |
| Trial protocol           | DE HU GB CZ NL |
| Global end of trial date | 31 July 2019   |

**Results information**

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 16 August 2020 |
| First version publication date | 16 August 2020 |

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

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | MDCO-PCS-17-08 |
|-----------------------|----------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03400800 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | The Medicines Company   |
| Sponsor organisation address | 8 Sylvan Way, Parsippany, United States, NJ 07054   |
| Public contact               | Global Health Science Center , The Medicines Company, +1 9732906000, medical.information@themedco.com |
| Scientific contact           | Global Health Science Center , The Medicines Company, +1 9732906000, medical.information@themedco.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                       | 05 October 2019 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 31 July 2019    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 July 2019    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of inclisiran treatment on:

- LDL-C levels at Day 510
- Time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDL-C lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo.

Evidence for comparator:

Use of placebo is consistent with other investigational lipid lowering therapy Phase III designs, including the statins and the monoclonal antibody PCSK9 inhibitors. All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDL-C lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo. The use of placebo in this type of study is consistent with EU guidance on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3).

|   |                                  |
|---|----------------------------------|
| Actual start date of recruitment                          | 01 November 2017                 |
| Long term follow-up planned                               | Yes                              |
| Long term follow-up rationale                             | Safety, Efficacy, Ethical reason |
| Long term follow-up duration                              | 18 Months                        |
| Independent data monitoring committee (IDMC) involvement? | Yes                              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Poland: 717         |
| Country: Number of subjects enrolled | United Kingdom: 462 |
| Country: Number of subjects enrolled | Czech Republic: 21  |
| Country: Number of subjects enrolled | Germany: 83         |
| Country: Number of subjects enrolled | Hungary: 104        |
| Country: Number of subjects enrolled | South Africa: 121   |
| Country: Number of subjects enrolled | Ukraine: 109        |
| Worldwide total number of subjects   | 1617                |
| EEA total number of subjects         | 1387                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 733 |
| From 65 to 84 years                       | 884 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Not applicable

### Pre-assignment

Screening details:

Screening occurred prior to randomization and consisted of confirming eligibility and collecting baseline assessments. Subjects enrolled must have fasting triglyceride <4.52 mmol/L (<400 mg/dL) and serum LDL-C  $\geq$ 1.8 mmol/L ( $\geq$ 70 mg/dL) at screening.

### Pre-assignment period milestones

|                              |      |
|------------------------------|------|
| Number of subjects started   | 1617 |
| Number of subjects completed | 1617 |

### Period 1

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

Blinding implementation details:

As inclisiran may be visually distinguishable from placebo, blinded syringes were provided to all study sites and used to maintain the blind.

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Inclisiran |

Arm description:

Inclisiran sodium 300 mg

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | Inclisiran                          |
| Investigational medicinal product code | ALN-60212                           |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for solution for injection |
| Routes of administration               | Subcutaneous use                    |

Dosage and administration details:

Inclisiran sodium 300 milligrams (mg) was administered as a subcutaneous injection on Day 1, Day 90 then every 6 months.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo arm

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

Dosage and administration details:

Placebo was administered as a subcutaneous injection on Day 1, Day 90 then every 6 months.

| <b>Number of subjects in period 1</b> | Inclisiran | Placebo |
|---------------------------------------|------------|---------|
| Started                               | 810        | 807     |
| Completed                             | 772        | 770     |
| Not completed                         | 38         | 37      |
| Consent withdrawn by subject          | 13         | 17      |
| Physician decision                    | 1          | 1       |
| Adverse Event                         | 4          | -       |
| Death                                 | 14         | 15      |
| Not specified                         | -          | 1       |
| Lost to follow-up                     | 6          | 3       |

## Baseline characteristics

### Reporting groups

|  |            |
|--|------------|
| Reporting group title                                    | Inclisiran |
| Reporting group description:<br>Inclisiran sodium 300 mg |            |
| Reporting group title                                    | Placebo    |
| Reporting group description:<br>Placebo arm              |            |

| Reporting group values                | Inclisiran | Placebo | Total |
|---------------------------------------|------------|---------|-------|
| Number of subjects                    | 810        | 807     | 1617  |
| Age categorical<br>Units: Subjects    |            |         |       |
| Adults (18-64 years)                  | 367        | 366     | 733   |
| Adults (65 - 74 years)                | 354        | 327     | 681   |
| Adults (from 75 years)                | 89         | 114     | 203   |
| Gender categorical<br>Units: Subjects |            |         |       |
| Female                                | 231        | 226     | 457   |
| Male                                  | 579        | 581     | 1160  |

### Subject analysis sets

|   |                    |
|---|--------------------|
| Subject analysis set title  | Inclisiran         |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Inclisiran Intention-to-treat population |                    |
| Subject analysis set title  | Placebo            |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Placebo Intention-to-treat population    |                    |

| Reporting group values                | Inclisiran | Placebo |  |
|---------------------------------------|------------|---------|--|
| Number of subjects                    | 810        | 807     |  |
| Age categorical<br>Units: Subjects    |            |         |  |
| Adults (18-64 years)                  | 367        | 366     |  |
| Adults (65 - 74 years)                | 354        | 327     |  |
| Adults (from 75 years)                | 89         | 114     |  |
| Gender categorical<br>Units: Subjects |            |         |  |
| Female                                | 231        | 226     |  |
| Male                                  | 579        | 581     |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Inclisiran         |
| Reporting group description:<br>Inclisiran sodium 300 mg                      |                    |
| Reporting group title   | Placebo            |
| Reporting group description:<br>Placebo arm                                   |                    |
| Subject analysis set title  | Inclisiran         |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Inclisiran Intention-to-treat population |                    |
| Subject analysis set title  | Placebo            |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Placebo Intention-to-treat population    |                    |

### Primary: Percentage Change in LDL-C From Baseline to Day 510

|   |   |
|---|---|
| End point title                             | Percentage Change in LDL-C From Baseline to Day 510 |
| End point description:                      |   |
| End point type                              | Primary   |
| End point timeframe:<br>Baseline to Day 510 |   |

| End point values                             | Inclisiran               | Placebo            | Inclisiran               | Placebo              |
|--|--------------------------|--------------------|--------------------------|----------------------|
| Subject group type                           | Reporting group          | Reporting group    | Subject analysis set     | Subject analysis set |
| Number of subjects analysed                  | 810                      | 807                | 810                      | 807                  |
| Units: % change                              |                          |                    |                          |                      |
| least squares mean (confidence interval 95%) | -49.3 (-51.22 to -47.48) | 4.2 (1.62 to 6.69) | -49.3 (-51.22 to -47.48) | 4.2 (1.62 to 6.69)   |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Percentage Change in LDL-C from Baseline - Day 510 |
| Statistical analysis description:<br>Difference in the percentage change in LDL-C from baseline to Day 510 between inclisiran and placebo arms |  |
| Comparison groups  | Inclisiran v Placebo                               |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 1617                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.0001                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -53.5                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -56.7                          |
| upper limit                             | -50.3                          |

### Primary: Time-adjusted Percent Change in LDL-C Levels from Baseline After Day 90 to up Day 540

|                           |   |
|---------------------------|---|
| End point title           | Time-adjusted Percent Change in LDL-C Levels from Baseline After Day 90 to up Day 540 |
| End point description:    |   |
| End point type            | Primary   |
| End point timeframe:      |   |
| Baseline, Day 90, Day 540 |   |

| End point values                             | Inclisiran                | Placebo             | Inclisiran                | Placebo              |
|--|---------------------------|---------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group     | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                 | 810                       | 807                  |
| Units: % change                              |                           |                     |                           |                      |
| least squares mean (confidence interval 95%) | -45.82 (-47.52 to -44.13) | 3.35 (1.65 to 5.05) | -45.82 (-47.52 to -44.13) | 3.35 (1.65 to 5.05)  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Percentage Change in LDL-C from Day 90 to Day 540 |
| Statistical analysis description:  |   |
| Difference in time-adjusted percentage change in LDL-C Levels From Baseline After Day 90 and up to Day 540 between inclisiran and placebo arms |   |
| Comparison groups  | Inclisiran v Placebo                              |
| Number of subjects included in analysis  | 1617  |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | superiority                                       |
| P-value  | < 0.0001  |
| Method   | ANCOVA  |
| Parameter estimate   | Mean difference (final values)                    |
| Point estimate   | -49.17  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -51.57  |
| upper limit         | -46.77  |

### Secondary: Absolute Change in LDL-C from Baseline to Day 510

|                        |   |
|------------------------|---|
| End point title        | Absolute Change in LDL-C from Baseline to Day 510 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline, Day 510      |   |

| End point values                             | Inclisiran                | Placebo              | Inclisiran                | Placebo              |
|--|---------------------------|----------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group      | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                  | 810                       | 807                  |
| Units: % change                              |                           |                      |                           |                      |
| least squares mean (confidence interval 95%) | -50.91 (-53.14 to -48.67) | 0.96 (-1.26 to 3.18) | -50.91 (-53.14 to -48.67) | 0.96 (0.96 to 3.18)  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Absolute Change in LDL-C From Baseline To Day 510 |
| Statistical analysis description:   |   |
| Difference in Absolute Change in LDL-C From Baseline To Day 510 between inclisiran and placebo arms |   |
| Comparison groups   | Inclisiran v Placebo                              |
| Number of subjects included in analysis   | 1617  |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | superiority                                       |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)                    |
| Point estimate  | -51.87  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -55.01  |
| upper limit   | -48.72  |

### Secondary: Time-adjusted Absolute Change in LDL-C From Baseline After Day 90

**and up to Day 540**

|                 |   |
|-----------------|---|
| End point title | Time-adjusted Absolute Change in LDL-C From Baseline After Day 90 and up to Day 540 |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline, Day 90, Day 540

| End point values                             | Inclisiran                | Placebo              | Inclisiran                | Placebo              |
|--|---------------------------|----------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group      | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                  | 810                       | 807                  |
| Units: % change                              |                           |                      |                           |                      |
| least squares mean (confidence interval 95%) | -48.63 (-50.37 to -46.89) | 0.31 (-1.42 to 2.04) | -48.63 (-50.37 to -46.89) | 0.31 (-1.42 to 2.04) |

**Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Absolute Change in Time-adjusted Change in LDL-C |
|-----------------------------------|--|

Statistical analysis description:

Difference in the change in time-adjusted LDL-C after Day 90 and up to Day 540, between inclisiran and placebo groups

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Inclisiran v Placebo           |
| Number of subjects included in analysis | 1617                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.0001                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -48.94                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -51.39                         |
| upper limit                             | -46.48                         |

**Secondary: Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510**

|                 |   |
|-----------------|---|
| End point title | Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510 |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline, Day 510

| <b>End point values</b>                      | Inclisiran                | Placebo                | Inclisiran                | Placebo                |
|--|---------------------------|------------------------|---------------------------|------------------------|
| Subject group type                           | Reporting group           | Reporting group        | Subject analysis set      | Subject analysis set   |
| Number of subjects analysed                  | 810                       | 807                    | 810                       | 807                    |
| Units: & change                              |                           |                        |                           |                        |
| least squares mean (confidence interval 95%) | -63.64 (-65.55 to -61.74) | 15.62 (13.72 to 17.53) | -63.64 (-65.55 to -61.74) | 15.62 (13.72 to 17.53) |

## Statistical analyses

| <b>Statistical analysis title</b>  | Percentage change in PCSK9 from Baseline - Day 510 |
|--|--|
| Statistical analysis description:  |  |
| Difference in percentage change in PCSK9 from baseline to Day 510, between inclisiran and placebo arms |  |
| Comparison groups  | Inclisiran v Placebo                               |
| Number of subjects included in analysis  | 1617   |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | superiority  |
| P-value  | < 0.0001   |
| Method   | ANCOVA   |
| Parameter estimate   | Mean difference (final values)                     |
| Point estimate   | -79.27   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -81.97   |
| upper limit  | -76.57   |

## Secondary: Percentange Change in Total Cholesterol From Baseline to Day 510

|                        |   |
|------------------------|---|
| End point title        | Percentage Change in Total Cholesterol From Baseline to Day 510 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline, Day 510      |   |

| End point values                             | Inclisiran                | Placebo             | Inclisiran                | Placebo              |
|--|---------------------------|---------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group     | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                 | 810                       | 807                  |
| Units: % change                              |                           |                     |                           |                      |
| least squares mean (confidence interval 95%) | -28.00 (-29.40 to -26.60) | 1.79 (0.38 to 3.21) | -28.00 (-29.40 to -26.60) | 1.79 (0.38 to 3.21)  |

## Statistical analyses

| Statistical analysis title   | Percentage change in Total Cholesterol |
|--|--|
| Statistical analysis description:  |  |
| Difference in the percentage change in total cholesterol from baseline to Day 510, between inclisiran and placebo arms |  |
| Comparison groups  | Inclisiran v Placebo                   |
| Number of subjects included in analysis  | 1617                                   |
| Analysis specification   | Pre-specified                          |
| Analysis type  | superiority                            |
| P-value  | < 0.001                                |
| Method   | ANCOVA                                 |
| Parameter estimate   | Mean difference (final values)         |
| Point estimate   | -29.79                                 |
| Confidence interval  |  |
| level  | 95 %                                   |
| sides  | 2-sided                                |
| lower limit  | -31.78                                 |
| upper limit  | -27.81                                 |

## Secondary: Percentage change in Apolipoprotein B From Baseline to Day 510

| End point title        | Percentage change in Apolipoprotein B From Baseline to Day 510 |
|------------------------|--|
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline, Day 510      |  |

| End point values                             | Inclisiran                | Placebo              | Inclisiran                | Placebo              |
|--|---------------------------|----------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group      | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                  | 810                       | 807                  |
| Units: % Change                              |                           |                      |                           |                      |
| least squares mean (confidence interval 95%) | -38.15 (-39.76 to -36.54) | 0.79 (-0.82 to 2.41) | -38.15 (-39.76 to -36.54) | 0.79 (-0.82 to 2.41) |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Percentage change in Apo B form Baseline - Day 510 |
| Statistical analysis description:<br>Difference in the percentage change in Apolipoprotein B (ApoB) from baseline to Day 510 |  |
| Comparison groups  | Placebo v Inclisiran                               |
| Number of subjects included in analysis  | 1617   |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | superiority  |
| P-value  | < 0.0001   |
| Method   | ANCOVA   |
| Parameter estimate   | Mean difference (final values)                     |
| Point estimate   | -38.94   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -41.21   |
| upper limit  | -36.67   |

## Secondary: Percentage Change in Non-HDL-C From Baseline to Day 510

|   |   |
|---|---|
| End point title                           | Percentage Change in Non-HDL-C From Baseline to Day 510 |
| End point description:                    |   |
| End point type                            | Secondary   |
| End point timeframe:<br>Baseline, Day 510 |   |

| End point values                             | Inclisiran                | Placebo             | Inclisiran                | Placebo              |
|--|---------------------------|---------------------|---------------------------|----------------------|
| Subject group type                           | Reporting group           | Reporting group     | Subject analysis set      | Subject analysis set |
| Number of subjects analysed                  | 810                       | 807                 | 810                       | 807                  |
| Units: % change                              |                           |                     |                           |                      |
| least squares mean (confidence interval 95%) | -41.16 (-43.09 to -39.24) | 2.15 (0.22 to 4.09) | -41.16 (-43.09 to -39.24) | 2.15 (0.22 to 4.09)  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Percentage Change in Non-HDL-C: baseline - Day 510 |
| Statistical analysis description:  |  |
| Difference in the percentage change in Non-HDL-C from baseline to Day 510, between inclisiran and placebo arms |  |
| Comparison groups  | Inclisiran v Placebo                               |
| Number of subjects included in analysis  | 1617   |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | superiority  |
| P-value  | < 0.0001   |
| Method   | ANCOVA   |
| Parameter estimate   | Mean difference (final values)                     |
| Point estimate   | -43.32   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -46  |
| upper limit  | -40.6  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

17 months

Adverse event reporting additional description:

The Efficacy population was comprised of 807 (Placebo) and 810 (Inclisiran) for a total of 1617 subjects. The Safety population consisted of 804 (Placebo) and 811 (Inclisiran). Two randomized subjects (Placebo) were not dosed. One placebo subject received inclisiran at Day 450 so was reallocated to the inclisiran group for safety.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Inclisiran |
|-----------------------|------------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events  | Inclisiran         | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed   | 181 / 811 (22.32%) | 181 / 804 (22.51%) |  |
| number of deaths (all causes)                                       | 14                 | 15                 |  |
| number of deaths resulting from adverse events                      | 0                  | 0                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Acute myeloid leukaemia   |                    |                    |  |
| subjects affected / exposed   | 1 / 811 (0.12%)    | 0 / 804 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Adenocarcinoma gastric  |                    |                    |  |
| subjects affected / exposed   | 1 / 811 (0.12%)    | 1 / 804 (0.12%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Bladder cancer  |                    |                    |  |
| subjects affected / exposed   | 1 / 811 (0.12%)    | 1 / 804 (0.12%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 1              |  |
| Bladder neoplasm  |                    |                    |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder transitional cell carcinoma             |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder transitional cell carcinoma recurrent   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carcinoid tumour of the stomach                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clear cell renal cell carcinoma                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endometrial adenocarcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal carcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular carcinoma                        |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intestinal adenocarcinoma                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laryngeal cancer stage IV                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lentigo maligna                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Linitis plastica                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung carcinoma cell type unspecified recurrent  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Metastases to liver                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metastatic carcinoma of the bladder             |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Non-Hodgkin's lymphoma                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal carcinoma                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Oral neoplasm                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral nerve sheath tumour malignant        |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 6 / 804 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostate cancer metastatic                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal adenocarcinoma                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cancer metastatic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cell carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Salivary gland cancer                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of the cervix           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheal neoplasm                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic dissection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic stenosis                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood pressure inadequately controlled          |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Extremity necrosis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Granulomatosis with polyangiitis                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Iliac artery embolism                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 7 / 811 (0.86%) | 8 / 804 (1.00%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery occlusion                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery stenosis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral vascular disorder                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thromboangiitis obliterans                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vasculitis                                      |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Leg amputation                                       |                 |                 |  |
| subjects affected / exposed                          | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Cardiac death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 2           |  |
| Exercise tolerance decreased                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Impaired healing                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 4 / 811 (0.49%) | 8 / 804 (1.00%) |  |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 8           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Sudden cardiac death                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Vascular stent occlusion                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular stent restenosis                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Sarcoidosis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (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 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic prolapse                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Prostatomegaly                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Choking   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 3 / 804 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Emphysema                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nasal polyps                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary fibrosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sleep apnoea syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device loosening                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Liver function test increased                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| 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  |                 |                 |  |
| Acetabulum fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arterial bypass occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary vascular graft occlusion               |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Head injury                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incision site pain                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Limb injury                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial reocclusion                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periprocedural myocardial infarction            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint injury                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural complication                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural hypotension                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural pain                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| 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                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Soft tissue injury                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 3 / 804 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic fracture                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%)  | 2 / 804 (0.25%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angina pectoris                                 |                  |                  |  |
| subjects affected / exposed                     | 14 / 811 (1.73%) | 13 / 804 (1.62%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 0 / 14           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute myocardial infarction                     |                  |                  |  |
| subjects affected / exposed                     | 5 / 811 (0.62%)  | 18 / 804 (2.24%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 21           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Angina unstable                                 |                  |                  |  |
| subjects affected / exposed                     | 11 / 811 (1.36%) | 11 / 804 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic valve stenosis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%)  | 0 / 804 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arrhythmia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 811 (0.00%)  | 1 / 804 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 10 / 811 (1.23%) | 6 / 804 (0.75%)  |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrial flutter                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%)  | 0 / 804 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atrioventricular block complete                 |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular block second degree            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 6 / 804 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 5 / 811 (0.62%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 8 / 811 (0.99%) | 11 / 804 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Coronary artery insufficiency                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Coronary artery occlusion                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Coronary artery stenosis                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypertensive heart disease                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Left ventricular dysfunction                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Left ventricular failure                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Mitral valve incompetence                       |                 |                  |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 0 / 804 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myocardial infarction                           |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 811 (0.62%) | 4 / 804 (0.50%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 4 / 811 (0.49%) | 5 / 804 (0.62%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Palpitations                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paroxysmal arrhythmia                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Silent myocardial infarction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular fibrillation                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain injury                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia Alzheimer's type                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial paralysis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised tonic-clonic seizure                |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial venous sinus thrombosis            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 3 / 804 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Lacunar stroke                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy peripheral                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral sensorimotor neuropathy              |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphadenopathy mediastinal                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| 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                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal detachment                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Chronic gastritis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diaphragmatic hernia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 10          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulum intestinal haemorrhagic            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erosive oesophagitis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incarcerated umbilical hernia                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 811 (0.25%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal spasm                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis chronic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis necrotising                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peptic ulcer                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal prolapse                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Volvulus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis erosive                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Biliary dilatation                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 811 (0.37%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Pyoderma gangrenosum                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 5 / 811 (0.62%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic kidney disease                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| End stage renal disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glomerulonephritis membranous                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrotic syndrome                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urethral stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Hypopituitarism                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Facet joint syndrome                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inclusion body myositis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc degeneration                |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc space narrowing             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 3 / 804 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periarthritis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psoriatic arthropathy                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotator cuff syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Soft tissue necrosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal osteoarthritis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spondylolisthesis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic lupus erythematosus                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Undifferentiated connective tissue disease      |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthropathy                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chondrocalcinosis pyrophosphate                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Costochondritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest wall abscess                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gallbladder abscess                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gallbladder empyema                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gangrene  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infectious pleural effusion                                   |                 |                 |  |
| subjects affected / exposed                                   | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 811 (0.12%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Influenza   |                 |                 |  |
| subjects affected / exposed                                   | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Intervertebral discitis                                       |                 |                 |  |
| subjects affected / exposed                                   | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection                             |                 |                 |  |
| subjects affected / exposed                                   | 3 / 811 (0.37%) | 3 / 804 (0.37%) |  |
| occurrences causally related to treatment / all               | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 1           |  |
| Neuroborreliosis  |                 |                 |  |
| subjects affected / exposed                                   | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pathogen resistance   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pneumonia   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 9 / 811 (1.11%) | 7 / 804 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia pneumococcal                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 2 / 804 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Sialoadenitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 811 (0.37%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (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>Dehydration</b>                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Diabetes mellitus</b>                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Diabetic ketoacidosis</b>                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hyperglycaemia</b>                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypoglycaemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 811 (0.25%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypovolaemia</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 811 (0.12%) | 0 / 804 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Type 2 diabetes mellitus</b>                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 811 (0.00%) | 1 / 804 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



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

| <b>Non-serious adverse events</b>                     | Inclisiran         | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 331 / 811 (40.81%) | 319 / 804 (39.68%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed                           | 53 / 811 (6.54%)   | 54 / 804 (6.72%)   |  |
| occurrences (all)                                     | 60                 | 59                 |  |
| Musculoskeletal and connective tissue disorders       |                    |                    |  |
| Arthralgia  |                    |                    |  |
| subjects affected / exposed                           | 47 / 811 (5.80%)   | 32 / 804 (3.98%)   |  |
| occurrences (all)                                     | 56                 | 37                 |  |
| Infections and infestations                           |                    |                    |  |
| Nasopharyngitis                                       |                    |                    |  |
| subjects affected / exposed                           | 91 / 811 (11.22%)  | 90 / 804 (11.19%)  |  |
| occurrences (all)                                     | 105                | 110                |  |
| Upper respiratory tract infection                     |                    |                    |  |
| subjects affected / exposed                           | 52 / 811 (6.41%)   | 49 / 804 (6.09%)   |  |
| occurrences (all)                                     | 59                 | 57                 |  |
| Metabolism and nutrition disorders                    |                    |                    |  |
| Diabetes mellitus                                     |                    |                    |  |
| subjects affected / exposed                           | 88 / 811 (10.85%)  | 94 / 804 (11.69%)  |  |
| occurrences (all)                                     | 101                | 100                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 18 December 2017 | Clarifications to the protocol synopsis and main body were included in order to address comments received from the FDA. The exclusion criterion #3, site training requirements and statistics sections were revised.<br>Changes were made to the following sections:<br>Synopsis-Exclusion Criteria, Synopsis-Statistical Methods, Section 4.3-Exclusion Criteria, Section 10.3.2.1-Intent-to-Treat (ITT) Population, Section 10.3.2.2-Modified Intent-to-Treat (mITT) Population, Section 10.3.4-Missing Data Handling, Section 10.4.3-Efficacy Analysis, 10.4.3.1.1-Sensitivity Analysis for Primary Efficacy Endpoints and 10.4.3.2-Secondary Efficacy Endpoint.<br>Administrative amendments were made to the protocol.   |
| 31 January 2019  | Synopsis, Section 2.1, Section 3.3, Section 3.4, Section 7.2.1, Section 10.4.3.1 to account for refinement in the description of time adjusted analyses of LDL-C. Section 6.1. Table 2. Section 6.4, Section 6.6, Section 6.8, Section 7.1.8.8 to clarify the plan to test for ADA.<br>Section 6.1. Table 2. Schedule of Assessments to align with Health Authority feedback for wider visit windows.<br>Section 10.3.2.2., Section 10.4.1., Section 10.4.3 to add to account for the addition of a new analysis set (Full Analysis Set).<br>Section 10.3.3. Analysis Windows and Baseline to clarify that analysis windows will be defined to maximize the amount of data that are included in the analysis models and that full details will be provided in the Statistical Analysis Plan.<br>Synopsis, Section 10.3.4, Section 10.4.3.1, Section 10.4.3.1.1. Missing Data Handling to align approach to missing data handling with Health Authority feedback and that details are provided in the Statistical Analysis Plan.<br>Section 10.4.4.2. Laboratory Tests to add analyses for clinically significant laboratory parameters. |

Notes:

### 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.

Not applicable.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32187462>