



## Clinical trial results:

### Long-term Safety and Tolerability of REGN727/SAR236553 in High Cardiovascular Risk Patients with Hypercholesterolemia not Adequately Controlled with Their Lipid Modifying Therapy: a Randomized, Double-blind, Placebo-controlled Study

#### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2011-002806-59                            |
| Trial protocol           | BE FI SE ES PT DE CZ NO GB NL HU IT DK BG |
| Global end of trial date | 19 November 2014                          |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 16 April 2016 |
| First version publication date | 16 April 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | LTS11717 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                               |
|------------------------------------|-------------------------------|
| ISRCTN number                      | -                             |
| ClinicalTrials.gov id (NCT number) | NCT01507831                   |
| WHO universal trial number (UTN)   | U1111-1121-3928               |
| Other trial identifiers            | Study Name: ODYSSEY LONG TERM |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi aventis recherche & développement   |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380                              |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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                       | 24 December 2014 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 November 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of SAR236553(REGN727) in high cardiovascular (CV) risk subjects with hypercholesterolemia not adequately controlled with their lipid modifying therapy (LMT).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

All subjects received a stable dose of statin (rosuvastatin, simvastatin or atorvastatin) with or without other LMT as clinically indicated throughout the duration of study.

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 06 January 2012 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Netherlands: 68     |
| Country: Number of subjects enrolled | Norway: 48          |
| Country: Number of subjects enrolled | Poland: 146         |
| Country: Number of subjects enrolled | Portugal: 8         |
| Country: Number of subjects enrolled | Spain: 92           |
| Country: Number of subjects enrolled | Sweden: 32          |
| Country: Number of subjects enrolled | United Kingdom: 484 |
| Country: Number of subjects enrolled | Belgium: 25         |
| Country: Number of subjects enrolled | Bulgaria: 78        |
| Country: Number of subjects enrolled | Czech Republic: 20  |
| Country: Number of subjects enrolled | Denmark: 16         |
| Country: Number of subjects enrolled | Finland: 20         |
| Country: Number of subjects enrolled | France: 87          |
| Country: Number of subjects enrolled | Germany: 139        |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Hungary: 78            |
| Country: Number of subjects enrolled | Italy: 37              |
| Country: Number of subjects enrolled | Argentina: 28          |
| Country: Number of subjects enrolled | Canada: 63             |
| Country: Number of subjects enrolled | Chile: 2               |
| Country: Number of subjects enrolled | Colombia: 2            |
| Country: Number of subjects enrolled | Israel: 8              |
| Country: Number of subjects enrolled | Mexico: 50             |
| Country: Number of subjects enrolled | Romania: 44            |
| Country: Number of subjects enrolled | Russian Federation: 28 |
| Country: Number of subjects enrolled | South Africa: 215      |
| Country: Number of subjects enrolled | Ukraine: 38            |
| Country: Number of subjects enrolled | United States: 485     |
| Worldwide total number of subjects   | 2341                   |
| EEA total number of subjects         | 1422                   |

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)                      | 1474 |
| From 65 to 84 years                       | 859  |
| 85 years and over                         | 8    |

## Subject disposition

### Recruitment

#### Recruitment details:

The study was conducted at 320 centers in 27 countries. Overall, 5144 subjects were screened between January 2012 and March 2013, 2801 of whom were screen failures. Screen failures were mainly due to exclusion criteria met. In addition 2 subjects received study drug but did not undergo randomization. They were excluded from analysis.

### Pre-assignment

#### Screening details:

Randomization was stratified as per diagnosis of heterozygous familial hypercholesterolemia (heFH), prior history of myocardial infarction (MI) or ischemic stroke, intensity of statin treatment and geographic region. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:2 ratio (placebo:alirocumab).

### Period 1

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

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Placebo Q2W |

#### Arm description:

Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks.

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

#### Dosage and administration details:

Placebo matched to alirocumab administered as SC injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Alirocumab 150 mg Q2W |
|------------------|-----------------------|

#### Arm description:

Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Alirocumab                                   |
| Investigational medicinal product code | SAR236553, REGN727                           |
| Other name                             | Praluent                                     |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

#### Dosage and administration details:

Alirocumab administered as SC injection in the abdomen, thigh, or outer area of the upper arm by self-injection or by another designated person.

| <b>Number of subjects in period 1</b>    | Placebo Q2W | Alirocumab 150 mg Q2W |
|--|-------------|-----------------------|
| Started                                  | 788         | 1553                  |
| Treated                                  | 788         | 1550                  |
| Completed                                | 595         | 1113                  |
| Not completed                            | 193         | 440                   |
| Physician decision                       | -           | 4                     |
| Adverse Event                            | 48          | 113                   |
| Selection criteria finally not met       | -           | 1                     |
| Poor compliance to protocol              | 38          | 60                    |
| Site closure                             | -           | 3                     |
| Last visit outside protocol visit window | 51          | 143                   |
| Consent withdrawn by subject             | 34          | 72                    |
| Randomized but not treated               | -           | 3                     |
| Death                                    | 6           | 2                     |
| Subject moved                            | 5           | 19                    |
| Unspecified                              | 3           | 6                     |
| Lost to follow-up                        | 3           | -                     |
| Related to study drug administration     | 5           | 14                    |

## Baseline characteristics

### Reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Placebo Q2W           |
| Reporting group description:<br>Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks. |                       |
| Reporting group title  | Alirocumab 150 mg Q2W |
| Reporting group description:<br>Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.   |                       |

| Reporting group values | Placebo Q2W | Alirocumab 150 mg Q2W | Total |
|------------------------|-------------|-----------------------|-------|
| Number of subjects     | 788         | 1553                  | 2341  |
| Age categorical        |             |                       |       |
| Units: Subjects        |             |                       |       |

|  |         |         |      |
|--|---------|---------|------|
| Age continuous   |         |         |      |
| Units: years   |         |         |      |
| arithmetic mean  | 60.6    | 60.4    | -    |
| standard deviation   | ± 10.4  | ± 10.4  | -    |
| Gender categorical   |         |         |      |
| Units: Subjects  |         |         |      |
| Female   | 314     | 570     | 884  |
| Male   | 474     | 983     | 1457 |
| Calculated LDL-C in mg/dL  |         |         |      |
| Calculated LDL-C in mg/dL from Friedewald formula (LDL-C = Total cholesterol - High-density lipoprotein cholesterol - [Triglyceride/5]). |         |         |      |
| Units: mg/dL   |         |         |      |
| arithmetic mean  | 121.9   | 122.7   | -    |
| standard deviation   | ± 41.4  | ± 42.6  | -    |
| Calculated LDL-C in mmol/L   |         |         |      |
| Units: mmol/L  |         |         |      |
| arithmetic mean  | 3.157   | 3.178   | -    |
| standard deviation   | ± 1.073 | ± 1.102 | -    |

## End points

### End points reporting groups

|  |                       |
|--|-----------------------|
| Reporting group title  | Placebo Q2W           |
| Reporting group description:<br>Placebo (for alirocumab) subcutaneous (SC) injection every 2 weeks (Q2W) added to stable lipid modifying therapy (LMT) for 78 weeks. |                       |
| Reporting group title  | Alirocumab 150 mg Q2W |
| Reporting group description:<br>Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.   |                       |

### Primary: Percentage of Subjects Who Experienced Adverse Events (AEs)

|  |   |
|--|---|
| End point title  | Percentage of Subjects Who Experienced Adverse Events |
| End point description:<br>Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of study drug up to the last dose of study drug +70 days). Safety population: all randomized subjects who received at least one dose or part of a dose of a study drug (treated). |   |
| End point type   | Primary   |
| End point timeframe:<br>Up to 10 weeks after last study drug administration (maximum of 86 weeks)  |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Safety analyses were descriptive in nature.  |   |

| End point values                            | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|---|-----------------|-----------------------|--|--|
| Subject group type                          | Reporting group | Reporting group       |  |  |
| Number of subjects analysed                 | 788             | 1550                  |  |  |
| Units: percentage of subjects               |                 |                       |  |  |
| number (not applicable)                     |                 |                       |  |  |
| Any AE                                      | 82.5            | 81                    |  |  |
| Any Serious AE                              | 19.5            | 18.7                  |  |  |
| Any AE leading to death                     | 1.3             | 0.5                   |  |  |
| Any AE leading to treatment discontinuation | 5.8             | 7.2                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-Treat (ITT) Analysis

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-Treat (ITT) Analysis |
| End point description:<br>Adjusted least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect |  |

model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment.

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From Baseline to Week 52 |           |

| End point values                    | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 780             | 1530                  |  |  |
| Units: percent change               |                 |                       |  |  |
| least squares mean (standard error) | 0.8 (± 1)       | -61 (± 0.7)           |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:   |                                      |
| Alirocumab group was compared to placebo group using an appropriate contrast statement. |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[2]</sup>              |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS mean difference                   |
| Point estimate  | -61.9                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -64.3                                |
| upper limit   | -59.4                                |

Notes:

[2] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Calculated LDL-C at Week 24 - On-Treatment Analysis

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Calculated LDL-C at Week 24 - On-Treatment Analysis |
| End point description:   |   |
| Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection) (on-treatment analysis). Modified ITT (mITT) population: all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Baseline to Week 52   |   |



| <b>End point values</b>             | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 777             | 1523                  |  |  |
| Units: percent change               |                 |                       |  |  |
| least squares mean (standard error) | 0.7 (± 1)       | -62.8 (± 0.7)         |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | Alirocumab 150 mg Q2W vs Placebo Q2W |
|-----------------------------------|--------------------------------------|
|-----------------------------------|--------------------------------------|

Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2300                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.0001 <sup>[3]</sup>             |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | LS Mean Difference                  |
| Point estimate                          | -63.5                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -65.9                               |
| upper limit                             | -61.2                               |

Notes:

[3] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 780             | 1530                  |  |  |
| Units: Percent Change               |                 |                       |  |  |
| least squares mean (standard error) | 1.5 (± 1)       | -63.3 (± 0.7)         |  |  |

## Statistical analyses

| Statistical analysis title   | Alirocumab 150 mg Q2W vs Placebo Q2W |
|--|--------------------------------------|
| Statistical analysis description:  |                                      |
| Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups  | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis  | 2310                                 |
| Analysis specification   | Pre-specified                        |
| Analysis type  | superiority                          |
| P-value  | < 0.0001 <sup>[4]</sup>              |
| Method   | Mixed models analysis                |
| Parameter estimate   | LS Mean Difference                   |
| Point estimate   | -64.8                                |
| Confidence interval  |                                      |
| level  | 95 %                                 |
| sides  | 2-sided                              |
| lower limit  | -67.2                                |
| upper limit  | -62.4                                |

Notes:

[4] - Threshold for significance ≤ 0.05.

## Secondary: Percent Change From Baseline in Calculated LDL-C at Week 12 - On-Treatment Analysis

| End point title   | Percent Change From Baseline in Calculated LDL-C at Week 12 - On-Treatment Analysis |
|---|---|
| End point description:  |   |
| Adjusted LS means and standard errors at Week 12 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). mITT population. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From Baseline to Week 52  |   |

| End point values                    | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 777             | 1523                  |  |  |
| Units: percent change               |                 |                       |  |  |
| least squares mean (standard error) | 1.4 (± 1)       | -64.2 (± 0.7)         |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2300                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[5]</sup>              |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -65.5                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -67.9                                |
| upper limit   | -63.2                                |

Notes:

[5] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Measured LDL-C at Week 24 - ITT Analysis

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Measured LDL-C at Week 24 - ITT Analysis |
| End point description:<br>Measured LDL-C values via beta quantification method. Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline measured LDL-C value on- or off-treatment. |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Baseline to Week 52   |  |

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 652              | 1278                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 3.5 ( $\pm$ 1.1) | -57.8 ( $\pm$ 0.8)    |  |  |

## Statistical analyses

|  |                                      |
|--|--------------------------------------|
| <b>Statistical analysis title</b>  | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:  |                                      |
| Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups  | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis  | 1930                                 |
| Analysis specification   | Pre-specified                        |
| Analysis type  | superiority                          |
| P-value  | < 0.0001 <sup>[6]</sup>              |
| Method   | Mixed models analysis                |
| Parameter estimate   | LS Mean Difference                   |
| Point estimate   | -61.3                                |
| Confidence interval  |                                      |
| level  | 95 %                                 |
| sides  | 2-sided                              |
| lower limit  | -64                                  |
| upper limit  | -58.5                                |

Notes:

[6] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Apolipoprotein (Apo) B at Week 24 - ITT Analysis

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Apolipoprotein (Apo) B at Week 24 - ITT Analysis |
| End point description:   |  |
| Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment (Apo B ITT population). |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From Baseline to Week 52   |  |

| End point values                    | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 753             | 1468                  |  |  |
| Units: percent change               |                 |                       |  |  |
| least squares mean (standard error) | 1.2 ( $\pm$ 1)  | -52.8 ( $\pm$ 0.7)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2221                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[7]</sup>              |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -54                                  |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -56.3                                |
| upper limit   | -51.7                                |

Notes:

[7] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Apo B at Week 24 - On-Treatment Analysis

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in Apo B at Week 24 - On-Treatment Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). Subjects of the mITT population with one baseline and at least one post-baseline Apo-B value on-treatment (Apo B mITT population). |  |
| End point type  | Secondary  |
| End point timeframe:<br>From Baseline to Week 52  |  |

|                                     |                  |                       |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| <b>End point values</b>             | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 743              | 1444                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 1.2 ( $\pm$ 0.9) | -54.3 ( $\pm$ 0.7)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2187                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 [8]                         |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -55.5                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -57.7                                |
| upper limit   | -53.2                                |

Notes:

[8] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 24 - ITT Analysis

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Week 24 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment (non-HDL-C ITT population). |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Baseline to Week 52   |  |

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 780              | 1530                  |  |  |
| Units: Percent Change               |                  |                       |  |  |
| least squares mean (standard error) | 0.7 ( $\pm$ 0.9) | -51.6 ( $\pm$ 0.6)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[9]</sup>              |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -52.3                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -54.4                                |
| upper limit   | -50.2                                |

Notes:

[9] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Non-HDL-C at Week 24 - On-Treatment Analysis

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in Non-HDL-C at Week 24 - On-Treatment Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 24 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). Subjects of the mITT population with one baseline and at least one post-baseline non-HDL-C value on-treatment (non-HDL-C mITT population). |  |
| End point type  | Secondary  |
| End point timeframe:<br>From Baseline to Week 52  |  |

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 777              | 1523                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 0.6 ( $\pm$ 0.9) | -53.1 ( $\pm$ 0.6)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2300                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[10]</sup>             |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -53.7                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -55.7                                |
| upper limit   | -51.6                                |

Notes:

[10] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline Total-C value on- or off-treatment (Total-C ITT population). |   |
| End point type   | Secondary   |
| End point timeframe:<br>From Baseline to Week 52   |   |

| End point values                    | Placebo Q2W       | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-------------------|-----------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group       |  |  |
| Number of subjects analysed         | 780               | 1530                  |  |  |
| Units: percent change               |                   |                       |  |  |
| least squares mean (standard error) | -0.3 ( $\pm$ 0.7) | -37.8 ( $\pm$ 0.5)    |  |  |



## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[11]</sup>             |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -37.5                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -39.1                                |
| upper limit   | -35.9                                |

Notes:

[11] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Apo B at Week 12 - ITT Analysis

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Apo B at Week 12 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo B ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 52  |   |

|                                     |                  |                       |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| <b>End point values</b>             | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 753              | 1468                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 0.5 ( $\pm$ 0.9) | -55.5 ( $\pm$ 0.7)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2221                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[12]</sup>             |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | -56                                  |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -58.3                                |
| upper limit   | -53.7                                |

Notes:

[12] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Non-HDL-C ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 52  |   |

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 780              | 1530                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 0.9 ( $\pm$ 0.8) | -53.7 ( $\pm$ 0.6)    |  |  |

### Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 2310                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[13]</sup> |
| Method                                  | Mixed models analysis    |
| Parameter estimate                      | LS Mean Difference       |
| Point estimate                          | -54.6                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -56.6                    |
| upper limit                             | -52.6                    |

Notes:

[13] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percent Change From Baseline in Total-C at Week 12 - ITT Analysis

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Total-C at Week 12 - ITT Analysis |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Total-C ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W       | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-------------------|-----------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group       |  |  |
| Number of subjects analysed         | 780               | 1530                  |  |  |
| Units: percent change               |                   |                       |  |  |
| least squares mean (standard error) | 0.2 ( $\pm 0.6$ ) | -38.8 ( $\pm 0.4$ )   |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2310                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.0001 <sup>[14]</sup>            |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | LS Mean Difference                  |
| Point estimate                          | -39                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -40.4   |
| upper limit         | -37.5   |

Notes:

[14] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percentage of Very High Cardiovascular (CV) Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

|                 |   |
|-----------------|---|
| End point title | Percentage of Very High Cardiovascular (CV) Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis |
|-----------------|---|

End point description:

Very high CV risk: Heterozygous Familial Hypercholesterolemia(heFH) subjects with coronary heart disease(CHD) or CHD risk equivalents or non- Familial Hypercholesterolemia(FH). High CV risk: heFH subjects without CHD or CHD risk equivalents. CHD risk equivalent: peripheral arterial disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate, 30 to <60 ml/minute/1.73 m<sup>2</sup> of body-surface area), or diabetes mellitus + 2 or more additional risk factors (hypertension; ankle-brachial index of  $\leq 0.90$ ; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or family history of premature CHD). Adjusted percentages at Week 24 were obtained from multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment were included in imputation model. ITT population.

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

End point timeframe:

Up to Week 52

| End point values              | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 780             | 1530                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 8.5             | 80.7                  |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

|                   |                                     |
|-------------------|-------------------------------------|
| Comparison groups | Alirocumab 150 mg Q2W v Placebo Q2W |
|-------------------|-------------------------------------|

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 2310                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[15]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 71.5                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 51.6                     |
| upper limit                             | 99.1                     |

Notes:

[15] - Threshold for significance  $\leq 0.05$ .

---

**Secondary: Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis**

---

|                 |   |
|-----------------|---|
| End point title | Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis |
|-----------------|---|

End point description:

Adjusted percentages at Week 24 were from multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). mITT population.

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

End point timeframe:

Up to Week 52

---

| End point values              | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 777             | 1523                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 8.5             | 82.8                  |  |  |

**Statistical analyses**

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Alirocumab 150 mg Q2W vs Placebo Q2W |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

|                   |                                     |
|-------------------|-------------------------------------|
| Comparison groups | Alirocumab 150 mg Q2W v Placebo Q2W |
|-------------------|-------------------------------------|

---

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 2300                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[16]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 93.4                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 66.1                     |
| upper limit                             | 132                      |

Notes:

[16] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted percentages at Week 24 were obtained from multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment were included in the imputation model. ITT population.

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

End point timeframe:

Up to Week 52

| End point values              | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 780             | 1530                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 8               | 79.3                  |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2310                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.0001 <sup>[17]</sup>            |
| Method                                  | Regression, Logistic                |
| Parameter estimate                      | Odds ratio (OR)                     |
| Point estimate                          | 74.6                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 53.3    |
| upper limit         | 104.4   |

Notes:

[17] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis

|   |   |
|---|---|
| End point title   | Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis |
| End point description:  |   |
| Adjusted percentages at Week 24 from multiple imputation approach model including available post-baseline data from Week 4 to Week 52 (i.e. up to 21 days after last injection). mITT population. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Up to Week 52   |   |

| End point values              | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 777             | 1523                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 8               | 81.2                  |  |  |

### Statistical analyses

|  |                                      |
|--|--------------------------------------|
| Statistical analysis title   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:  |                                      |
| Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by logistic regression model. |                                      |
| Comparison groups  | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis  | 2300                                 |
| Analysis specification   | Pre-specified                        |
| Analysis type  | superiority                          |
| P-value  | < 0.0001 <sup>[18]</sup>             |
| Method   | Regression, Logistic                 |
| Parameter estimate   | Odds ratio (OR)                      |
| Point estimate   | 97.3                                 |
| Confidence interval  |                                      |
| level  | 95 %                                 |
| sides  | 2-sided                              |
| lower limit  | 68.2                                 |
| upper limit  | 138.9                                |

Notes:

[18] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in Lipoprotein (a) at Week 24 - ITT Analysis

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Lipoprotein (a) at Week 24 - ITT Analysis |
|-----------------|---|

End point description:

Adjusted means and standard errors at Week 24 were obtained from multiple imputation approach followed by robust regression model for handling of missing data. All available post-baseline data from Week 4 to Week 52 regardless of status on-or off-treatment were included in the imputation model. ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values                 | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|----------------------------------|------------------|-----------------------|--|--|
| Subject group type               | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed      | 780              | 1530                  |  |  |
| Units: percent change            |                  |                       |  |  |
| arithmetic mean (standard error) | -3.7 ( $\pm 1$ ) | -29.3 ( $\pm 0.7$ )   |  |  |

## Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model.

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2310                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | $< 0.0001$ <sup>[19]</sup>          |
| Method                                  | Regression, Robust                  |
| Parameter estimate                      | Adjusted Mean Difference            |
| Point estimate                          | -25.6                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -28.1                               |
| upper limit                             | -23.1                               |

Notes:

[19] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in HDL-C at Week 24 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in HDL-C at Week 24 - ITT |
|-----------------|--|



## End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment (HDL-C ITT population).

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

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W       | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-------------------|-----------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group       |  |  |
| Number of subjects analysed         | 780               | 1530                  |  |  |
| Units: percent change               |                   |                       |  |  |
| least squares mean (standard error) | -0.6 ( $\pm$ 0.5) | 4 ( $\pm$ 0.4)        |  |  |

## Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2310                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.0001 <sup>[20]</sup>            |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | LS Mean Difference                  |
| Point estimate                          | 4.6                                 |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 3.3                                 |
| upper limit                             | 5.9                                 |

Notes:

[20] - Threshold for significance  $\leq$  0.05.

### Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis |
|-----------------|---|

End point description:

Adjusted means and standard errors at Week 24 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. ITT population.

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

End point timeframe:  
From Baseline to Week 52

| End point values                 | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|----------------------------------|------------------|-----------------------|--|--|
| Subject group type               | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed      | 780              | 1530                  |  |  |
| Units: percent change            |                  |                       |  |  |
| arithmetic mean (standard error) | 1.8 ( $\pm$ 1.2) | -15.6 ( $\pm$ 0.8)    |  |  |

## Statistical analyses

| Statistical analysis title  | Alirocumab 150 mg Q2W vs Placebo Q2W |
|---|--------------------------------------|
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model. |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[21]</sup>             |
| Method  | Regression, Robust                   |
| Parameter estimate  | Adjusted Mean Difference             |
| Point estimate  | -17.3                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -20.1                                |
| upper limit   | -14.6                                |

Notes:

[21] - Threshold for significance  $\leq$  0.05.

## Secondary: Percent Change From Baseline in Apo A1 at Week 24 - ITT Analysis

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Apo A1 at Week 24 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Subjects of the ITT population with one baseline and at least one post-baseline Apo A1 value on- or off-treatment (Apo A1 ITT population). |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Baseline to Week 52   |  |

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 753              | 1468                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 1.2 ( $\pm$ 0.6) | 4 ( $\pm$ 0.4)        |  |  |

## Statistical analyses

| Statistical analysis title  | Alirocumab 150 mg Q2W vs Placebo Q2W |
|---|--------------------------------------|
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2221                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[22]</sup>             |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | 2.9                                  |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | 1.6                                  |
| upper limit   | 4.2                                  |

Notes:

[22] - Threshold for significance  $\leq$  0.05.

## Secondary: Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis

| End point title   | Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis |
|---|---|
| End point description:<br>Adjusted means and standard errors at Week 12 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 52 regardless of status on-or off-treatment. ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 52  |   |

| End point values                 | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|----------------------------------|-----------------|-----------------------|--|--|
| Subject group type               | Reporting group | Reporting group       |  |  |
| Number of subjects analysed      | 780             | 1530                  |  |  |
| Units: percent change            |                 |                       |  |  |
| arithmetic mean (standard error) | -3.1 ( $\pm$ 1) | -28.2 ( $\pm$ 0.7)    |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model. |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[23]</sup>             |
| Method  | Regression, Robust                   |
| Parameter estimate  | Adjusted Mean Difference             |
| Point estimate  | -25.1                                |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | -27.4                                |
| upper limit   | -22.7                                |

Notes:

[23] - Threshold for significance  $\leq 0.05$ .

## Secondary: Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. HDL-C ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 52  |   |

|                                     |                  |                       |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| <b>End point values</b>             | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 780              | 1530                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 0.2 ( $\pm$ 0.5) | 5.8 ( $\pm$ 0.4)      |  |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |
| Number of subjects included in analysis   | 2310                                 |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | < 0.0001 <sup>[24]</sup>             |
| Method  | Mixed models analysis                |
| Parameter estimate  | LS Mean Difference                   |
| Point estimate  | 5.6                                  |
| Confidence interval   |                                      |
| level   | 95 %                                 |
| sides   | 2-sided                              |
| lower limit   | 4.3                                  |
| upper limit   | 6.8                                  |

Notes:

[24] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis |
| End point description:<br>Adjusted means and standard errors at Week 12 from multiple imputation approach followed by robust regression model including all available post-baseline data from Week 4 to Week 52 regardless of status on-or off-treatment. ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 52  |   |

| End point values                 | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|----------------------------------|------------------|-----------------------|--|--|
| Subject group type               | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed      | 780              | 1530                  |  |  |
| Units: percent change            |                  |                       |  |  |
| arithmetic mean (standard error) | 1.2 ( $\pm$ 1.1) | -16.7 ( $\pm$ 0.8)    |  |  |

### Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>   | Alirocumab 150 mg Q2W vs Placebo Q2W |
| Statistical analysis description:<br>Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant). Multiple imputation approach followed by a robust regression model. |                                      |
| Comparison groups   | Alirocumab 150 mg Q2W v Placebo Q2W  |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 2310                     |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[25]</sup> |
| Method                                  | Regression, Robust       |
| Parameter estimate                      | Adjusted Mean Difference |
| Point estimate                          | -17.9                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -20.5                    |
| upper limit                             | -15.3                    |

Notes:

[25] - Threshold for significance  $\leq 0.05$ .

### Secondary: Percent Change From Baseline in Apo A1 at Week 12 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Apo A1 at Week 12 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. Apo A1 ITT population.

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

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W       | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-------------------|-----------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group       |  |  |
| Number of subjects analysed         | 753               | 1468                  |  |  |
| Units: percent change               |                   |                       |  |  |
| least squares mean (standard error) | 0.6 ( $\pm 0.5$ ) | 4.6 ( $\pm 0.3$ )     |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Alirocumab 150 mg Q2W vs Placebo Q2W |
|----------------------------|--------------------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (only performed if the previous endpoint was statistically significant).

|   |                                     |
|---|-------------------------------------|
| Comparison groups                       | Alirocumab 150 mg Q2W v Placebo Q2W |
| Number of subjects included in analysis | 2221                                |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | < 0.0001 <sup>[26]</sup>            |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | LS Mean Difference                  |
| Point estimate                          | 4                                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 2.8     |
| upper limit         | 5.2     |

Notes:

[26] - Threshold for significance  $\leq 0.05$ .

### Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 52 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 52 from MMRM model including all available post-baseline data from Week 4 to Week 52 regardless of status on- or off-treatment. ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W       | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-------------------|-----------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group       |  |  |
| Number of subjects analysed         | 780               | 1530                  |  |  |
| Units: percent change               |                   |                       |  |  |
| least squares mean (standard error) | 4.4 ( $\pm 1.2$ ) | -56.8 ( $\pm 0.8$ )   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 52 - On-Treatment Analysis

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 52 - On-Treatment Analysis |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 52 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 52 (i.e. up to 21 days after last injection). mITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From Baseline to Week 52

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 777              | 1523                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 4.6 ( $\pm$ 1.1) | -59.9 ( $\pm$ 0.8)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 78 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 78 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 78 from MMRM model including all available post-baseline data from Week 4 to Week 78 regardless of status on- or off-treatment. ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From Baseline to Week 78

| End point values                    | Placebo Q2W      | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|------------------|-----------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group       |  |  |
| Number of subjects analysed         | 780              | 1530                  |  |  |
| Units: percent change               |                  |                       |  |  |
| least squares mean (standard error) | 3.6 ( $\pm$ 1.3) | -52.4 ( $\pm$ 0.9)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change From Baseline in Calculated LDL-C at Week 78 - On-Treatment Analysis

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Calculated LDL-C at Week 78 - On-Treatment Analysis |
|-----------------|---|

End point description:

Adjusted LS means and standard errors at Week 78 from MMRM model including available post-baseline on-treatment data from Week 4 to Week 78 (i.e. up to 21 days after last injection). mITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From Baseline to Week 78



| End point values                    | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type                  | Reporting group | Reporting group       |  |  |
| Number of subjects analysed         | 777             | 1523                  |  |  |
| Units: percent change               |                 |                       |  |  |
| least squares mean (standard error) | 3.9 (± 1.2)     | -58 (± 0.9)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percentage of Subjects Who Experienced Cardiovascular (CV) Events

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Experienced Cardiovascular (CV) Events |
|-----------------|---|

End point description:

CV events included coronary heart disease (CHD) death; non-fatal myocardial infarction (MI); fatal and non-fatal ischemic stroke; unstable angina requiring hospitalization; congestive heart failure (CHF) requiring hospitalization; ischemia-driven coronary revascularization procedure. Reported events are CV events as confirmed by an independent Clinical Events Committee (CEC) that occurred during the treatment emergent period ( i.e. from first dose up to the last dose of study drug + 70 days). Safety population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 10 weeks after last study drug administration (maximum of 86 weeks)

| End point values              | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 788             | 1550                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 5.1             | 4.6                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage of Subjects Who Experienced Major Adverse CV Events

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Who Experienced Major Adverse CV Events |
|-----------------|--|

End point description:

Major adverse CV events were defined as all adverse CV events except Congestive heart failure (CHF) requiring hospitalization; and ischemia-driven coronary revascularization procedure. Safety population.

|   |          |
|---|----------|
| End point type  | Post-hoc |
| End point timeframe:  |          |
| Up to 10 weeks after last study drug administration (maximum of 86 weeks) |          |

| <b>End point values</b>       | Placebo Q2W     | Alirocumab 150 mg Q2W |  |  |
|-------------------------------|-----------------|-----------------------|--|--|
| Subject group type            | Reporting group | Reporting group       |  |  |
| Number of subjects analysed   | 788             | 1550                  |  |  |
| Units: percentage of subjects |                 |                       |  |  |
| number (not applicable)       | 3.3             | 1.7                   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 86 post-treatment follow-up visit) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during 'the treatment emergent period' (from the first dose of study drug up to the last dose of study drug + 70 days).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Placebo Q2W |
|-----------------------|-------------|

Reporting group description:

Placebo (for alirocumab) SC injection Q2W added to stable LMT for 78 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Alirocumab 150 Q2W |
|-----------------------|--------------------|

Reporting group description:

Alirocumab 150 mg SC injection Q2W added to stable LMT for 78 weeks.

| Serious adverse events  | Placebo Q2W        | Alirocumab 150 Q2W  |  |
|---|--------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                    |                     |  |
| subjects affected / exposed   | 154 / 788 (19.54%) | 290 / 1550 (18.71%) |  |
| number of deaths (all causes)                                       | 8                  | 7                   |  |
| number of deaths resulting from adverse events                      |                    |                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                     |  |
| Acute Myeloid Leukaemia   |                    |                     |  |
| subjects affected / exposed   | 1 / 788 (0.13%)    | 0 / 1550 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 1              | 0 / 0               |  |
| Adenocarcinoma Of Colon   |                    |                     |  |
| subjects affected / exposed   | 1 / 788 (0.13%)    | 0 / 1550 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0               |  |
| B-Cell Lymphoma   |                    |                     |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Basal Cell Carcinoma                            |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 8 / 1550 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Benign Ovarian Tumour                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bladder Cancer                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Breast Cancer                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Choroid Melanoma                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Chronic Lymphocytic Leukaemia                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Colon Cancer                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ductal Adenocarcinoma Of Pancreas               |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Endometrial Cancer                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Endometrial Cancer Stage I                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Laryngeal Squamous Cell Carcinoma               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lip Squamous Cell Carcinoma                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Malignant Melanoma                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Neuroendocrine Carcinoma Metastatic             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Non-Hodgkin's Lymphoma Metastatic               |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Oesophageal Carcinoma                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pancreatic Carcinoma                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Pancreatic Carcinoma Metastatic                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pleomorphic Liposarcoma                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 3 / 788 (0.38%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Prostate Cancer Metastatic                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Prostate Cancer Recurrent                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rectal Adenocarcinoma                           |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Cancer                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Skin Cancer                                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Squamous Cell Carcinoma                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Squamous Cell Carcinoma Of Lung                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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 Skin                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Squamous Cell Carcinoma Of The Oral Cavity      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Tongue Cancer Metastatic                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Vascular disorders                              |                 |                  |  |
| Aortic Aneurysm                                 |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Aortic Aneurysm Rupture                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Aortic Dissection                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Deep Vein Thrombosis                            |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Extremity Necrosis                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Femoral Artery Aneurysm                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypertension                                    |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypertensive Crisis                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypotension                                     |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypovolaemic Shock                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Iliac Artery Occlusion                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lymphocele                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peripheral Arterial Occlusive Disease           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 4 / 1550 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peripheral Artery Stenosis                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 2 / 788 (0.25%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peripheral Vascular Disorder                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Subclavian Artery Stenosis                      |                 |                  |  |

|  |                 |                  |  |
|--|-----------------|------------------|--|
| subjects affected / exposed                          | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Thrombophlebitis                                     |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Pregnancy, puerperium and perinatal conditions       |                 |                  |  |
| Abortion Spontaneous                                 |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 0 / 1550 (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 |                 |                  |  |
| Chest Pain   |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Coronary Artery Restenosis                           |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Death  |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0            |  |
| Device Failure                                       |                 |                  |  |
| subjects affected / exposed                          | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Device Malfunction                                   |                 |                  |  |
| subjects affected / exposed                          | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| Multi-Organ Failure                             |                 |                   |  |
| subjects affected / exposed                     | 4 / 788 (0.51%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 1             |  |
| Non-Cardiac Chest Pain                          |                 |                   |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 13 / 1550 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Peripheral Artery Restenosis                    |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Immune system disorders                         |                 |                   |  |
| Cytokine Release Syndrome                       |                 |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Drug Hypersensitivity                           |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Hypersensitivity                                |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Reproductive system and breast disorders        |                 |                   |  |
| Galactorrhoea                                   |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Menorrhagia                                     |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Metrorrhagia                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ovarian Cyst                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Prostatomegaly                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Uterine Haemorrhage                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                 |                  |  |
| Acute Respiratory Distress Syndrome             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Acute Respiratory Failure                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Asthma  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchitis Chronic                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 6 / 788 (0.76%) | 4 / 1550 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyspnoea  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Epistaxis                                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pleural Effusion                                |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Laryngeal Oedema                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia Aspiration                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Pulmonary Embolism                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 6 / 1550 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary Hypertension                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                        | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Psychiatric disorders                              |                 |                  |  |
| Alcohol Abuse                                      |                 |                  |  |
| subjects affected / exposed                        | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Bipolar Disorder                                   |                 |                  |  |
| subjects affected / exposed                        | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all    | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Confusional State                                  |                 |                  |  |
| subjects affected / exposed                        | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all    | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Depression   |                 |                  |  |
| subjects affected / exposed                        | 2 / 788 (0.25%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all    | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Depression Suicidal                                |                 |                  |  |
| subjects affected / exposed                        | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Major Depression                                   |                 |                  |  |
| subjects affected / exposed                        | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all    | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Mental Disorder Due To A General Medical Condition |                 |                  |  |
| subjects affected / exposed                        | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0           | 0 / 0            |  |
| Mental Status Changes                              |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Panic Attack                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Suicidal Ideation                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Suicide Attempt                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Investigations                                  |                 |                  |  |
| Blood Creatine Phosphokinase Increased          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Electrocardiogram Qt Prolonged                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Electrocardiogram St Segment Depression         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Troponin Increased                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Injury, poisoning and procedural                |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| complications                                   |                 |                  |  |
| Abdominal Injury                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Accidental Overdose                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Arterial Injury                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Clavicle Fracture                               |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Contusion                                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Femur Fracture                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Fibula Fracture                                 |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hand Fracture                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hip Fracture                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Humerus Fracture                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intentional Overdose                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Joint Injury                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Laceration                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ligament Rupture                                |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Muscle Rupture                                  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Muscle Strain                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Post Procedural Haematoma                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Post Procedural Haematuria                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Postoperative Respiratory Failure               |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Spinal Cord Injury                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Tendon Rupture                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Tibia Fracture                                  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Traumatic Haematoma                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Traumatic Intracranial Haemorrhage              |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Vascular Pseudoaneurysm                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Wrist Fracture                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                 |                  |  |
| Hypertrophic Cardiomyopathy                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Thyroglossal Cyst                               |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac disorders                               |                 |                  |  |
| Acute Coronary Syndrome                         |                 |                  |  |
| subjects affected / exposed                     | 6 / 788 (0.76%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Acute Myocardial Infarction                     |                  |                   |  |
| subjects affected / exposed                     | 11 / 788 (1.40%) | 9 / 1550 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 13           | 1 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1             |  |
| Angina Pectoris                                 |                  |                   |  |
| subjects affected / exposed                     | 6 / 788 (0.76%)  | 9 / 1550 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Angina Unstable                                 |                  |                   |  |
| subjects affected / exposed                     | 9 / 788 (1.14%)  | 29 / 1550 (1.87%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 31            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aortic Valve Stenosis                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%)  | 2 / 1550 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriosclerosis Coronary Artery                |                  |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%)  | 1 / 1550 (0.06%)  |  |
| 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                     | 7 / 788 (0.89%)  | 9 / 1550 (0.58%)  |  |
| occurrences causally related to treatment / all | 0 / 8            | 1 / 9             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrial Flutter                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%)  | 2 / 1550 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular Block                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%)  | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Atrioventricular Block Second Degree            |                  |                   |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Bradycardia                                     |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Cardiac Arrest                                  |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Cardiac Failure                                 |                 |                   |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 4 / 1550 (0.26%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1             |  |
| Cardiac Failure Chronic                         |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Cardiac Failure Congestive                      |                 |                   |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 4 / 1550 (0.26%)  |  |
| occurrences causally related to treatment / all | 0 / 4           | 3 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Cardiogenic Shock                               |                 |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Coronary Artery Disease                         |                 |                   |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 10 / 1550 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 2 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1             |  |
| Coronary Artery Occlusion                       |                 |                   |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Coronary Artery Stenosis                        |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dressler's Syndrome                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Extrasystoles                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypertensive Heart Disease                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Ischaemic Cardiomyopathy                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myocardial Infarction                           |                 |                  |  |
| subjects affected / exposed                     | 4 / 788 (0.51%) | 4 / 1550 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Myocardial Ischaemia                            |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Pleuropericarditis                              |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sick Sinus Syndrome                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Silent Myocardial Infarction                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sinus Bradycardia                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ventricular Fibrillation                        |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Ventricular Tachycardia                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nervous system disorders                        |                 |                  |  |
| Altered State Of Consciousness                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ataxia  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Brain Stem Infarction                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Carotid Arteriosclerosis                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Carotid Artery Stenosis                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Carpal Tunnel Syndrome                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cerebellar Infarction                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cerebral Haemorrhage                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cerebrovascular Accident                        |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Convulsion                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dementia  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Demyelination                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dysarthria                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Frontotemporal Dementia                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Generalised Tonic-Clonic Seizure                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemorrhagic Stroke                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Headache  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypoaesthesia                                   |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypoglycaemic Coma                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ischaemic Stroke                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 5 / 1550 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lacunar Infarction                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Loss Of Consciousness                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Migraine  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Miller Fisher Syndrome                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myoclonic Epilepsy                              |                 |                  |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Nerve Root Compression</b>                   |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Optic Neuritis</b>                           |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Parkinson's Disease</b>                      |                 |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Presyncope</b>                               |                 |                   |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Syncope</b>                                  |                 |                   |  |
| subjects affected / exposed                     | 6 / 788 (0.76%) | 11 / 1550 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Transient Ischaemic Attack</b>               |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 7 / 1550 (0.45%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                   |  |
| <b>Coagulopathy</b>                             |                 |                   |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| <b>Iron Deficiency Anaemia</b>                  |                 |                   |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Spontaneous Haematoma                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ear and labyrinth disorders                     |                 |                  |  |
| Vertigo   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Vertigo Positional                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Eye disorders                                   |                 |                  |  |
| Age-Related Macular Degeneration                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Blepharochalasis                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cataract  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diabetic Retinopathy                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Endocrine Ophthalmopathy                        |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Macular Hole                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Open Angle Glaucoma                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Retinal Artery Occlusion                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Retinal Haemorrhage                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Retinal Vein Occlusion                          |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Retinal Vein Thrombosis                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Visual Impairment                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Vitreous Detachment                             |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Gastrointestinal disorders</b>               |                 |                  |  |
| <b>Abdominal Adhesions</b>                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Abdominal Hernia</b>                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Abdominal Hernia Obstructive</b>             |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Abdominal Pain</b>                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Alcoholic Pancreatitis</b>                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Barrett's Oesophagus</b>                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Colitis</b>                                  |                 |                  |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Diarrhoea</b>                                |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Duodenal Ulcer Haemorrhage                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyspepsia                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastritis                                       |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastroduodenal Haemorrhage                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemorrhoids                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hiatus Hernia                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intestinal Obstruction                          |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intestinal Perforation                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intussusception                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Large Intestine Polyp                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nausea  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pancreatitis Acute                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pancreatitis Relapsing                          |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peptic Ulcer Haemorrhage                        |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Umbilical Hernia                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Upper Gastrointestinal Haemorrhage              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Vomiting  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatobiliary disorders                         |                 |                  |  |
| Bile Duct Stone                                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cholangitis                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cholecystitis Acute                             |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cholelithiasis                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Drug-Induced Liver Injury                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatic Steatosis                               |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hepatocellular Injury                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                 |                  |  |
| Angioedema                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dermatitis Allergic                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypersensitivity Vasculitis                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rash  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal and urinary disorders                     |                 |                  |  |
| Bladder Spasm                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Calculus Ureteric                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Calculus Urinary                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cystitis Interstitial                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diabetic Nephropathy                            |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haematuria                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypertonic Bladder                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nephrolithiasis                                 |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Artery Stenosis                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Failure Acute                             |                 |                  |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Failure Chronic                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Impairment                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal Pain                                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ureteric Stenosis                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urethral Stenosis                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urinary Retention                               |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Endocrine disorders                             |                 |                  |  |
| Thyrototoxic Crisis                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                 |                  |  |
| Ankylosing Spondylitis                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Arthritis                                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Back Pain                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intervertebral Disc Degeneration                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Intervertebral Disc Protrusion                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 4 / 1550 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Lumbar Spinal Stenosis                          |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Musculoskeletal Chest Pain                      |                 |                  |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Myositis  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Osteoarthritis                                  |                 |                  |  |
| subjects affected / exposed                     | 3 / 788 (0.38%) | 8 / 1550 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Osteochondrosis                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Osteonecrosis                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Polymyalgia Rheumatica                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rhabdomyolysis                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rotator Cuff Syndrome                           |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Spinal Column Stenosis                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Spinal Osteoarthritis                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Vertebral Foraminal Stenosis                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Infections and infestations                     |                 |                  |  |
| Bronchitis                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchopneumonia                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cellulitis                                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Clostridium Difficile Colitis                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Cystitis Viral                                  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Device Related Infection                        |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diabetic Foot Infection                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diverticulitis                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 4 / 1550 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastroenteritis                                 |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 5 / 1550 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastroenteritis Viral                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal Viral Infection                |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Groin Abscess                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Helicobacter Gastritis                          |                 |                  |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                                   | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Incision Site Infection                                       |                 |                  |  |
| subjects affected / exposed                                   | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Infective Exacerbation Of Chronic Obstructive Airways Disease |                 |                  |  |
| subjects affected / exposed                                   | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Influenza   |                 |                  |  |
| subjects affected / exposed                                   | 2 / 788 (0.25%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Labyrinthitis   |                 |                  |  |
| subjects affected / exposed                                   | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Lobar Pneumonia   |                 |                  |  |
| subjects affected / exposed                                   | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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                                   | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Lyme Disease  |                 |                  |  |
| subjects affected / exposed                                   | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0            |  |
| Neutropenic Sepsis  |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Osteomyelitis                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia                                       |                 |                  |  |
| subjects affected / exposed                     | 7 / 788 (0.89%) | 6 / 1550 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia Pneumococcal                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia Staphylococcal                        |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Post Procedural Sepsis                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Postoperative Wound Infection                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pyelonephritis                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pyelonephritis Acute                            |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sepsis  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 5 / 1550 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Septic Shock                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Upper Respiratory Tract Infection               |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urinary Tract Infection                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urinary Tract Infection Pseudomonal             |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urosepsis                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Wound Abscess                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Metabolism and nutrition disorders              |                 |                  |  |
| Dehydration                                     |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diabetes Mellitus                               |                 |                  |  |
| subjects affected / exposed                     | 2 / 788 (0.25%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diabetic Ketoacidosis                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyperglycaemia                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 2 / 1550 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyperkalaemia                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypoglycaemia                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 3 / 1550 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypokalaemia                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lactic Acidosis                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Lipomatosis                                     |                 |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| <b>Tumour Lysis Syndrome</b>                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 788 (0.13%) | 0 / 1550 (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 / 788 (0.00%) | 1 / 1550 (0.06%) |  |
| 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>                            | Placebo Q2W        | Alirocumab 150 Q2W  |  |
|--|--------------------|---------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                    |                     |  |
| subjects affected / exposed                                  | 366 / 788 (46.45%) | 707 / 1550 (45.61%) |  |
| <b>Nervous system disorders</b>                              |                    |                     |  |
| Headache   |                    |                     |  |
| subjects affected / exposed                                  | 44 / 788 (5.58%)   | 76 / 1550 (4.90%)   |  |
| occurrences (all)  | 47                 | 103                 |  |
| <b>General disorders and administration site conditions</b>  |                    |                     |  |
| Injection Site Reaction                                      |                    |                     |  |
| subjects affected / exposed                                  | 33 / 788 (4.19%)   | 91 / 1550 (5.87%)   |  |
| occurrences (all)  | 42                 | 184                 |  |
| <b>Gastrointestinal disorders</b>                            |                    |                     |  |
| Diarrhoea  |                    |                     |  |
| subjects affected / exposed                                  | 45 / 788 (5.71%)   | 89 / 1550 (5.74%)   |  |
| occurrences (all)  | 49                 | 112                 |  |
| <b>Musculoskeletal and connective tissue disorders</b>       |                    |                     |  |
| Arthralgia   |                    |                     |  |
| subjects affected / exposed                                  | 52 / 788 (6.60%)   | 80 / 1550 (5.16%)   |  |
| occurrences (all)  | 60                 | 87                  |  |
| Back Pain  |                    |                     |  |

|   |                           |                               |  |
|---|---------------------------|-------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                      | 52 / 788 (6.60%)<br>57    | 84 / 1550 (5.42%)<br>90       |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 23 / 788 (2.92%)<br>31    | 84 / 1550 (5.42%)<br>94       |  |
| Infections and infestations   |                           |                               |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 40 / 788 (5.08%)<br>45    | 83 / 1550 (5.35%)<br>102      |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 43 / 788 (5.46%)<br>53    | 88 / 1550 (5.68%)<br>103      |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 103 / 788 (13.07%)<br>143 | 209 / 1550<br>(13.48%)<br>267 |  |
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all) | 68 / 788 (8.63%)<br>79    | 114 / 1550 (7.35%)<br>136     |  |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)           | 54 / 788 (6.85%)<br>84    | 87 / 1550 (5.61%)<br>121      |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 29 November 2011 | Additional assessments were added for a possible significant lowering of LDL-C by alirocumab, including adrenal function monitoring and neurological examinations. The monitoring plan for LDL-C <25 mg/dL (0.65 mmol/L) was revised accordingly; Hepatitis C testing was added to the end of the treatment visit because some data suggested that proprotein convertase subtilisin kexin type 9 (PCSK9) negatively regulates CD81 levels ; An ophthalmologic sub-study in a sub-set of subjects and color vision testing in all subjects was added due to the observation of optic nerve degeneration and chorioretinal lesions in 26-week toxicology studies in rats and monkeys, respectively; Measured LDL-C via beta quantification method was added at key efficacy time points due to potential inaccuracies of calculated LDL-C, when the LDL-C level reaches <50 mg/dL (1.30 mmol/L); The exclusion criteria related to LDL-C was changed to <100 mg/dL (2.59 mmol/L), since this exclusion criterion was used in the phase 2 studies, it was viewed as more appropriate to keep the same inclusion criterion in LTS11717, when using the dose of 150 mg every 2 weeks.   |
| 11 May 2012      | The exclusion criteria of LDL-C >160 mg/dL (4.14 mmol/L) at screening and subject only on statin monotherapy without additional LMT were deleted. Such subjects could be included, but an explanation for no second LMT was to be provided; A guideline was added for medical work up for cases of low hemoglobin (post-baseline decrease of $\geq 15$ g/dL), and an algorithm was added for the identification of cases of hemolytic anemia; Clearer guidance was provided on follow-up of anti-alirocumab antibodies to maintain the integrity of the double-blind in the study; Criterion to meet an LDL-C rescue alert was modified; Clinical criteria for diagnosis of heFH for study eligibility was clarified; A CHD risk equivalent was added to include moderate chronic kidney disease as defined by estimated glomerular filtration rate (eGFR) 30 to <60 mL/min/1.73 m <sup>2</sup> for 3 months or more consistently with the 2011 Guidelines for the Management of Dyslipidaemias by The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society; Recent information on rare cases of hypersensitivity was added as well as details on monitoring, reporting, and collecting information to better document potential allergy events. |
| 12 November 2012 | Exclusion criterion related to LDL-C was changed from <100 mg/dL (2.59 mmol/L) to <70 mg/dL (1.81 mmol/L), thereby including a subject population that more completely represents the expected future clinical use of the compound; Assessments regarding vitamins A, D, and K as other fat soluble vitamins and gonadal hormones assessments were clarified to ensure the integrity of the blood sample and information collected; The description of adrenal function monitoring was updated to recommend early morning sampling to best evaluate this parameter.  |
| 26 February 2014 | The primary efficacy analysis population was changed to the ITT population and the statistical analysis methodology for the primary and secondary efficacy analysis endpoints was changed to ITT analysis performed on the ITT population and including all lipid values (on-treatment and off-treatment); The language regarding the recording of injection site reactions not related to IMP was updated to clarify the reporting of local injection site reactions.   |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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| Manual reclassification was done by the Sponsor for the "other reasons" of non-completion of study as specified in the electronic case report (eCRF) form. |
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Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25773378>