



## Clinical trial results:

### A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects With HIV and With Hyperlipidemia and/or Mixed Dyslipidemia

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2015-004735-12          |
| Trial protocol           | FR PT GB BE ES GR PL IT |
| Global end of trial date | 27 January 2020         |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 28 January 2021 |
| First version publication date | 28 January 2021 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20130286 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02833844 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Amgen Inc.  |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, California, United States,                     |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 27 January 2020 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 27 January 2020 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab administered once monthly (QM) compared with placebo QM on percent change from baseline in low density lipoprotein cholesterol (LDL-C) in human immunodeficiency virus (HIV)-positive subjects with hyperlipidemia and/or mixed dyslipidemia.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, and Food and Drug Administration regulations and guidelines set forth in 21 Code of Federal Regulations parts 11, 50, 54, 56, and 312. The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 22 May 2017 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 28      |
| Country: Number of subjects enrolled | South Africa: 20   |
| Country: Number of subjects enrolled | Belgium: 11        |
| Country: Number of subjects enrolled | France: 49         |
| Country: Number of subjects enrolled | Greece: 31         |
| Country: Number of subjects enrolled | Italy: 27          |
| Country: Number of subjects enrolled | Poland: 6          |
| Country: Number of subjects enrolled | Portugal: 24       |
| Country: Number of subjects enrolled | Romania: 18        |
| Country: Number of subjects enrolled | Spain: 24          |
| Country: Number of subjects enrolled | Switzerland: 25    |
| Country: Number of subjects enrolled | United Kingdom: 26 |
| Country: Number of subjects enrolled | Brazil: 25         |
| Country: Number of subjects enrolled | Canada: 32         |
| Country: Number of subjects enrolled | United States: 121 |
| Worldwide total number of subjects   | 467                |
| EEA total number of subjects         | 190                |

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)                      | 390 |
| From 65 to 84 years                       | 77  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 72 centers in Australia, Belgium, Brazil, Canada, France, Greece, Italy, Poland, Portugal, Romania, South Africa, Spain, Switzerland, United Kingdom, and United States. The first participant was enrolled on 22 May 2017, and the last participant was enrolled on 23 January 2019.

### Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to evolocumab or placebo, respectively, in a double-blind manner. Randomization was stratified by entry statin treatment and hepatitis C status.

### Period 1

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

Blinding implementation details:

Blinded individuals did not have access to unblinded information until the study was formally unblinded. Unblinding and potentially unblinding information was not distributed to the study team, investigators or subjects prior to the study being formally unblinded.

### Arms

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

Arm description:

Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 weeks.

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

Dosage and administration details:

Matching placebo administered QM at day 1 and weeks 4, 8, 12, 16, and 20 as an SC injection.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Double-Blind Evolocumab |
|------------------|-------------------------|

Arm description:

Double-blind evolocumab SC injection QM for 24 weeks.

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

Dosage and administration details:

Evolocumab 420 mg administered QM at day 1 and weeks 4, 8, 12, 16, and 20 as an SC injection.

| Number of subjects in period 1 | Double-Blind Placebo | Double-Blind Evolocumab |
|--------------------------------|----------------------|-------------------------|
| Started                        | 157                  | 310                     |
| Randomized and Treated         | 157                  | 307                     |
| Completed                      | 155                  | 303                     |
| Not completed                  | 2                    | 7                       |
| Consent withdrawn by subject   | 2                    | 3                       |
| Protocol deviation             | -                    | 4                       |

## Period 2

|                              |                   |
|------------------------------|-------------------|
| Period 2 title               | Open-Label Period |
| Is this the baseline period? | No                |
| Allocation method            | Not applicable    |
| Blinding used                | Not blinded       |

## Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Double-Blind Placebo/Open-Label Evolocumab |

### Arm description:

Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

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

### Dosage and administration details:

Evolocumab 420 mg QM at weeks 24, 28, 32, 36, 40, 44, and 48 as an SC injection.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Double-Blind Evolocumab/Open-Label Evolocumab |
|------------------|---|

### Arm description:

Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

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

### Dosage and administration details:

Evolocumab 420 mg QM at weeks 24, 28, 32, 36, 40, 44, and 48 as an SC injection.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Double-Blind Placebo/Open-Label Evolocumab | Double-Blind Evolocumab/Open-Label Evolocumab |
|---|--|---|
| Started   | 152  | 303   |
| Received Open-Label Study Drug                      | 152  | 299 <sup>[2]</sup>                            |
| Completed   | 150  | 301   |
| Not completed                                       | 2  | 2   |
| Adverse event, serious fatal                        | -  | 2   |
| Consent withdrawn by subject                        | 1  | -   |
| Lost to follow-up                                   | 1  | -   |

---

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 3 participants did not continue into the open-label period.

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

Justification: 4 participants did not receive open-label study drug.

## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Double-Blind Placebo    |
| Reporting group description:  |                         |
| Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 weeks. |                         |
| Reporting group title   | Double-Blind Evolocumab |
| Reporting group description:  |                         |
| Double-blind evolocumab SC injection QM for 24 weeks.                             |                         |

| Reporting group values | Double-Blind Placebo | Double-Blind Evolocumab | Total |
|------------------------|----------------------|-------------------------|-------|
| Number of subjects     | 157                  | 310                     | 467   |
| Age categorical        |                      |                         |       |
| Units: Subjects        |                      |                         |       |

|   |        |        |     |
|---|--------|--------|-----|
| Age Continuous  |        |        |     |
| Units: years  |        |        |     |
| arithmetic mean   | 56.2   | 56.5   |     |
| standard deviation  | ± 8.0  | ± 9.1  | -   |
| Sex: Female, Male   |        |        |     |
| Units:  |        |        |     |
| Female  | 37     | 45     | 82  |
| Male  | 120    | 265    | 385 |
| Ethnicity (NIH/OMB)   |        |        |     |
| Units: Subjects   |        |        |     |
| Hispanic or Latino  | 21     | 41     | 62  |
| Not Hispanic or Latino  | 136    | 269    | 405 |
| Unknown or Not Reported   | 0      | 0      | 0   |
| Race/Ethnicity, Customized  |        |        |     |
| Units: Subjects   |        |        |     |
| Asian   | 3      | 3      | 6   |
| Black or African American   | 25     | 54     | 79  |
| White   | 125    | 246    | 371 |
| Multiple Races  | 1      | 0      | 1   |
| Other, Not Specified  | 3      | 7      | 10  |
| Stratification Factor: Statin Use at Baseline                     |        |        |     |
| Units: Subjects   |        |        |     |
| Statin Use = Yes  | 128    | 256    | 384 |
| Statin Use = No   | 29     | 54     | 83  |
| Stratification Factor: Hepatitis C Virus (HCV) Status at Baseline |        |        |     |
| Units: Subjects   |        |        |     |
| HCV = Yes   | 7      | 10     | 17  |
| HCV = No  | 150    | 300    | 450 |
| Low-Density Lipoprotein Cholesterol (LDL-C)                       |        |        |     |
| Units: mg/dL  |        |        |     |
| arithmetic mean   | 133.26 | 133.25 |     |

|                    |             |             |   |
|--------------------|-------------|-------------|---|
| standard deviation | $\pm 39.97$ | $\pm 40.25$ | - |
|--------------------|-------------|-------------|---|



## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Double-Blind Placebo                          |
| Reporting group description:   |   |
| Double-blind placebo subcutaneous (SC) injection every 4 weeks (QM) for 24 weeks.  |   |
| Reporting group title  | Double-Blind Evolocumab                       |
| Reporting group description:   |   |
| Double-blind evolocumab SC injection QM for 24 weeks.  |   |
| Reporting group title  | Double-Blind Placebo/Open-Label Evolocumab    |
| Reporting group description:   |   |
| Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.    |   |
| Reporting group title  | Double-Blind Evolocumab/Open-Label Evolocumab |
| Reporting group description:   |   |
| Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks. |   |

### Primary: Percent Change From Baseline in LDL-C at Week 24

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in LDL-C at Week 24 |
| End point description:   |  |
| Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Baseline, Week 24  |  |

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 151                  | 295                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 1.68 ( $\pm$ 2.03)   | -55.23 ( $\pm$ 1.52)    |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis 1                         |
| Comparison groups          | Double-Blind Placebo v Double-Blind Evolocumab |

|   |  |
|---|--|
| Number of subjects included in analysis | 446                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.0001 <sup>[1]</sup>                |
| Method                                  | repeated measures linear effects model |
| Parameter estimate                      | treatment difference                   |
| Point estimate                          | -56.92                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -61.55                                 |
| upper limit                             | -52.28                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.36                                   |

Notes:

[1] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

### Secondary: Change From Baseline in LDL-C at Week 24

|                        |  |
|------------------------|--|
| End point title        | Change From Baseline in LDL-C at Week 24   |
| End point description: | Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |
| End point type         | Secondary  |
| End point timeframe:   | Baseline, Week 24  |

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 151                  | 295                     |  |  |
| Units: mg/dL                        |                      |                         |  |  |
| least squares mean (standard error) | -2.3 (± 3.1)         | -77.5 (± 2.3)           |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical Analysis 1                         |
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 446  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[2]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -75.2  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -82.1                      |
| upper limit          | -68.4                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.5                        |

Notes:

[2] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Secondary: Percentage of Participants Acheiving LDL-C < 70 mg/dL (1.8 mmol/L) at Week 24

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Acheiving LDL-C < 70 mg/dL (1.8 mmol/L) at Week 24 |
|-----------------|---|

End point description:

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

End point timeframe:

Week 24

| End point values                  | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-----------------------------------|----------------------|-------------------------|--|--|
| Subject group type                | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed       | 151                  | 296                     |  |  |
| Units: percentage of participants |                      |                         |  |  |
| number (confidence interval 95%)  | 7.9 (4.6 to 13.4)    | 73.3 (68.0 to 78.0)     |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

|   |  |
|---|--|
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 447  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 [3]                                   |
| Method                                  | Cochran-Mantel-Haenszel                        |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | 65.4   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 57.8   |
| upper limit                             | 71.1   |

Notes:

[3] - Based on Cochran-Mantel-Haenszel test stratified by statin use stratification factor. For testing, nonachievement was imputed for participants with a missing value.

### Secondary: Percentage of Participants With an LDL-C Response (50% Reduction of LDL-C From Baseline) at Week 24

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With an LDL-C Response (50% Reduction of LDL-C From Baseline) at Week 24 |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline, Week 24

| End point values                  | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-----------------------------------|----------------------|-------------------------|--|--|
| Subject group type                | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed       | 151                  | 295                     |  |  |
| Units: percentage of participants |                      |                         |  |  |
| number (confidence interval 95%)  | 0.7 (0.1 to 3.7)     | 72.5 (67.2 to 77.3)     |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

|                   |  |
|-------------------|--|
| Comparison groups | Double-Blind Placebo v Double-Blind Evolocumab |
|-------------------|--|

|   |     |
|---|-----|
| Number of subjects included in analysis | 446 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |                         |
|---------|-------------------------|
| P-value | < 0.0001 <sup>[4]</sup> |
|---------|-------------------------|

|        |                         |
|--------|-------------------------|
| Method | Cochran-Mantel-Haenszel |
|--------|-------------------------|

|                    |                      |
|--------------------|----------------------|
| Parameter estimate | treatment difference |
|--------------------|----------------------|

|                |      |
|----------------|------|
| Point estimate | 71.9 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 65.7 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 76.7 |
|-------------|------|

Notes:

[4] - Based on Cochran-Mantel-Haenszel test stratified by statin use stratification factor. For testing, nonachievement was imputed for participants with a missing value.

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

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (HDL-C) at Week 24 |
|-----------------|---|

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

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

End point timeframe:

Baseline, Week 24

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 152                  | 296                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 2.86 ( $\pm$ 1.74)   | -48.07 ( $\pm$ 1.31)    |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Statistical Analysis 1                         |
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 448  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[5]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -50.94   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -54.88   |
| upper limit                             | -46.99   |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 2.01   |

Notes:

[5] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Secondary: Percent Change From Baseline in Apolipoprotein B (ApoB) at Week 24

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Apolipoprotein B (ApoB) at Week 24 |
|-----------------|--|

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

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

End point timeframe:

Baseline, Week 24

| <b>End point values</b>             | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 153                  | 302                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 2.59 ( $\pm$ 1.50)   | -45.14 ( $\pm$ 1.13)    |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1                         |
|---|--|
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 455  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[6]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -47.73   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -51.11   |
| upper limit                             | -44.35   |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 1.72   |

Notes:

[6] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Secondary: Percent Change From Baseline in Total Cholesterol (TC) at Week 24

|                        |  |
|------------------------|--|
| End point title        | Percent Change From Baseline in Total Cholesterol (TC) at Week 24  |
| End point description: | Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline, Week 24      |  |

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 152                  | 296                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 2.34 ( $\pm$ 1.40)   | -35.78 ( $\pm$ 1.06)    |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1                         |
|---|--|
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 448  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[7]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -38.12   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -41.3  |
| upper limit                             | -34.94   |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 1.62   |

Notes:

[7] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Secondary: Percent Change From Baseline in Lipoprotein(a) (Lp[a]) at Week 24

| End point title  | Percent Change From Baseline in Lipoprotein(a) (Lp[a]) at Week 24 |
|--|---|
| End point description:   |   |
| Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Week 24  |   |

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 153                  | 302                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 10.35 ( $\pm$ 3.34)  | -16.44 ( $\pm$ 2.57)    |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                         |
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 455  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[8]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -26.78   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -34.17   |
| upper limit                             | -19.4  |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 3.76   |

Notes:

[8] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Secondary: Percent Change From Baseline in Triglycerides at Week 24

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Triglycerides at Week 24 |
| End point description:   |  |
| Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, Week 24  |  |

|                                     |                      |                         |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| <b>End point values</b>             | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 152                  | 296                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 13.21 (± 3.80)       | -9.25 (± 2.89)          |  |  |

## Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                         |
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 448  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[9]</sup>                        |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -22.46   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -31.03   |
| upper limit                             | -13.88   |
| Variability estimate                    | Standard error of the mean                     |
| Dispersion value                        | 4.36   |

Notes:

[9] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in HDL-C at Week 24 |
| End point description:   |  |
| Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.) |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Bseline, Week 24   |  |

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 152                  | 296                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 2.73 (± 1.57)        | 11.08 (± 1.20)          |  |  |

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis 1                         |
| Comparison groups                 | Double-Blind Placebo v Double-Blind Evolocumab |

|   |  |
|---|--|
| Number of subjects included in analysis | 448                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.0001 <sup>[10]</sup>               |
| Method                                  | repeated measures linear effects model |
| Parameter estimate                      | treatment difference                   |
| Point estimate                          | 8.36                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 4.83                                   |
| upper limit                             | 11.89                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 1.8                                    |

Notes:

[10] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

### Secondary: Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 24

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Week 24 |
|-----------------|--|

End point description:

Least squares mean is from the repeated measures model which includes treatment group, statin stratification factor, scheduled visit and the interaction of treatment with scheduled visit as covariates. (Hepatitis C stratification factor is not included in the model due to low participant numbers.)

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

End point timeframe:

Baseline, Week 24

| End point values                    | Double-Blind Placebo | Double-Blind Evolocumab |  |  |
|-------------------------------------|----------------------|-------------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group         |  |  |
| Number of subjects analysed         | 141                  | 284                     |  |  |
| Units: percent change               |                      |                         |  |  |
| least squares mean (standard error) | 12.34 (± 3.54)       | -9.81 (± 2.65)          |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                         |
| Comparison groups                       | Double-Blind Placebo v Double-Blind Evolocumab |
| Number of subjects included in analysis | 425  |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | < 0.0001 <sup>[11]</sup>                       |
| Method                                  | repeated measures linear effects model         |
| Parameter estimate                      | treatment difference                           |
| Point estimate                          | -22.15   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -30.04                     |
| upper limit          | -14.26                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 4.01                       |

Notes:

[11] - Multiplicity adjustment was based on the combination of sequential testing, the fallback procedure, and the Hochberg procedure.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Double-blind Treatment Period: From first dose of study drug to up to week 24. Open-label Extension Period: From first dose of study drug in the OLE up to 30 days after last dose, or end of study, whichever was earlier.

Adverse event reporting additional description:

Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Double-Blind Placebo |
|-----------------------|----------------------|

Reporting group description:

Double-blind placebo SC injection QM for 24 weeks.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Double-Blind Evolocumab |
|-----------------------|-------------------------|

Reporting group description:

Double-blind evolocumab SC injection QM for 24 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Double-Blind Placebo/Open-Label Evolocumab |
|-----------------------|--|

Reporting group description:

Participants originally randomized to placebo in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

|                       |   |
|-----------------------|---|
| Reporting group title | Double-Blind Evolocumab/Open-Label Evolocumab |
|-----------------------|---|

Reporting group description:

Participants originally randomized to evolocumab in the double-blind period then received open-label evolocumab 420 mg SC QM for 24 weeks.

| Serious adverse events  | Double-Blind Placebo | Double-Blind Evolocumab | Double-Blind Placebo/Open-Label Evolocumab |
|---|----------------------|-------------------------|--|
| Total subjects affected by serious adverse events                   |                      |                         |  |
| subjects affected / exposed   | 8 / 157 (5.10%)      | 10 / 307 (3.26%)        | 8 / 152 (5.26%)                            |
| number of deaths (all causes)                                       | 0                    | 0                       | 0  |
| number of deaths resulting from adverse events                      |                      |                         |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |                         |  |
| Lung adenocarcinoma   |                      |                         |  |
| subjects affected / exposed   | 0 / 157 (0.00%)      | 1 / 307 (0.33%)         | 1 / 152 (0.66%)                            |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 1                   | 0 / 1                                      |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0                   | 0 / 0                                      |
| Basal cell carcinoma  |                      |                         |  |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Basosquamous carcinoma of skin                       |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder cancer stage 0, with cancer in situ          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hair follicle tumour benign                          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Lipoma   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal cell carcinoma stage II                        |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Sarcomatoid carcinoma                                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Hypertensive emergency                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Anaphylactic reaction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchiectasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Angina pectoris                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriosclerosis coronary artery                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericarditis constrictive                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Migraine  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral artery thrombosis                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Partial seizures                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Blood loss anaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Anal fistula                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrooesophageal reflux disease                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Lipohypertrophy                                 |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                 |                 |
| Flank pain   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal chest pain                             |                 |                 |                 |
| subjects affected / exposed                            | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis   |                 |                 |                 |
| subjects affected / exposed                            | 2 / 157 (1.27%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Rhabdomyolysis   |                 |                 |                 |
| subjects affected / exposed                            | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc degeneration                       |                 |                 |                 |
| subjects affected / exposed                            | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>                     |                 |                 |                 |
| Staphylococcal infection                               |                 |                 |                 |
| subjects affected / exposed                            | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Tracheobronchitis                                      |                 |                 |                 |
| subjects affected / exposed                            | 0 / 157 (0.00%) | 1 / 307 (0.33%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastroenteritis bacterial                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Helicobacter gastritis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 1 / 152 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory syncytial virus bronchitis          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 307 (0.00%) | 0 / 152 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| Serious adverse events  | Double-Blind Evolocumab/Open-Label Evolocumab |  |  |
|---|---|--|--|
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 14 / 299 (4.68%)                              |  |  |
| number of deaths (all causes)                                       | 2   |  |  |
| number of deaths resulting from adverse events                      |   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Lung adenocarcinoma   |   |  |  |
| subjects affected / exposed   | 0 / 299 (0.00%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 0   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Basal cell carcinoma  |   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Basosquamous carcinoma of skin                       |                 |  |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Bladder cancer stage 0, with cancer in situ          |                 |  |  |
| subjects affected / exposed                          | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hair follicle tumour benign                          |                 |  |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Lipoma   |                 |  |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Renal cell carcinoma stage II                        |                 |  |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Sarcomatoid carcinoma                                |                 |  |  |
| subjects affected / exposed                          | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular disorders                                   |                 |  |  |
| Hypertensive emergency                               |                 |  |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Non-cardiac chest pain                          |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune system disorders                         |                 |  |  |
| Anaphylactic reaction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchiectasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Hip fracture                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Brain contusion                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Angina pectoris                                 |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Arteriosclerosis coronary artery                |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrial fibrillation                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure congestive                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Coronary artery stenosis                        |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Myocardial ischaemia                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ventricular tachycardia                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Angina unstable                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pericarditis constrictive                       |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Migraine  |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subarachnoid haemorrhage                        |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral artery thrombosis                      |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Partial seizures                                |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Presyncope                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Blood loss anaemia                              |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Anal fistula                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric ulcer                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrooesophageal reflux disease                |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis acute                             |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Lipohypertrophy                                 |                 |  |  |



|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| Flank pain   |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Musculoskeletal chest pain                             |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Osteoarthritis   |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Rhabdomyolysis   |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Intervertebral disc degeneration                       |                 |  |  |
| subjects affected / exposed                            | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| Staphylococcal infection                               |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Tracheobronchitis                                      |                 |  |  |
| subjects affected / exposed                            | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Gastroenteritis bacterial                       |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Helicobacter gastritis                          |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory syncytial virus bronchitis          |                 |  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Diabetic ketoacidosis                           |                 |  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Double-Blind<br>Placebo | Double-Blind<br>Evolocumab | Double-Blind<br>Placebo/Open-Label<br>Evolocumab |
|---|-------------------------|----------------------------|--|
| Total subjects affected by non-serious adverse events |                         |                            |  |
| subjects affected / exposed                           | 41 / 157 (26.11%)       | 78 / 307 (25.41%)          | 23 / 152 (15.13%)                                |
| Vascular disorders                                    |                         |                            |  |
| Hypertension  |                         |                            |  |
| subjects affected / exposed                           | 5 / 157 (3.18%)         | 0 / 307 (0.00%)            | 3 / 152 (1.97%)                                  |
| occurrences (all)                                     | 5                       | 0                          | 3  |
| Nervous system disorders                              |                         |                            |  |
| Headache  |                         |                            |  |

|  |                      |                        |                      |
|--|----------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                           | 5 / 157 (3.18%)<br>6 | 6 / 307 (1.95%)<br>6   | 3 / 152 (1.97%)<br>4 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 157 (0.00%)<br>0 | 7 / 307 (2.28%)<br>8   | 0 / 152 (0.00%)<br>0 |
| General disorders and administration<br>site conditions                    |                      |                        |                      |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)             | 5 / 157 (3.18%)<br>5 | 2 / 307 (0.65%)<br>2   | 0 / 152 (0.00%)<br>0 |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all) | 4 / 157 (2.55%)<br>4 | 12 / 307 (3.91%)<br>15 | 2 / 152 (1.32%)<br>2 |
| Gastrointestinal disorders   |                      |                        |                      |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)         | 4 / 157 (2.55%)<br>4 | 3 / 307 (0.98%)<br>3   | 0 / 152 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)              | 7 / 157 (4.46%)<br>7 | 11 / 307 (3.58%)<br>12 | 1 / 152 (0.66%)<br>1 |
| Musculoskeletal and connective tissue<br>disorders                         |                      |                        |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)             | 3 / 157 (1.91%)<br>3 | 9 / 307 (2.93%)<br>10  | 1 / 152 (0.66%)<br>1 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)              | 4 / 157 (2.55%)<br>4 | 12 / 307 (3.91%)<br>13 | 4 / 152 (2.63%)<br>4 |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                | 6 / 157 (3.82%)<br>6 | 6 / 307 (1.95%)<br>6   | 0 / 152 (0.00%)<br>0 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)      | 3 / 157 (1.91%)<br>3 | 7 / 307 (2.28%)<br>7   | 0 / 152 (0.00%)<br>0 |
| Infections and infestations  |                      |                        |                      |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)        | 2 / 157 (1.27%)<br>2 | 10 / 307 (3.26%)<br>10 | 6 / 152 (3.95%)<br>6 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 157 (2.55%)<br>4 | 7 / 307 (2.28%)<br>7 | 1 / 152 (0.66%)<br>1 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 157 (1.91%)<br>3 | 5 / 307 (1.63%)<br>5 | 2 / 152 (1.32%)<br>2 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 157 (0.64%)<br>1 | 1 / 307 (0.33%)<br>1 | 1 / 152 (0.66%)<br>1 |

| <b>Non-serious adverse events</b>   | Double-Blind<br>Evolocumab/Open-<br>Label Evolocumab |  |  |
|---|--|--|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 50 / 299 (16.72%)                                    |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 4 / 299 (1.34%)<br>4                                 |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 299 (0.33%)<br>1<br><br>1 / 299 (0.33%)<br>1     |  |  |
| General disorders and administration<br>site conditions<br>Chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all) | 1 / 299 (0.33%)<br>1<br><br>3 / 299 (1.00%)<br>3     |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea   | 0 / 299 (0.00%)<br>0                                 |  |  |

|   |                       |  |  |
|---|-----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                      | 8 / 299 (2.68%)<br>8  |  |  |
| Musculoskeletal and connective tissue disorders                                       |                       |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 299 (1.67%)<br>5  |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 299 (0.67%)<br>2  |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 299 (1.00%)<br>3  |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 299 (0.33%)<br>1  |  |  |
| Infections and infestations   |                       |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 9 / 299 (3.01%)<br>9  |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 299 (1.67%)<br>5  |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 7 / 299 (2.34%)<br>7  |  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 299 (2.68%)<br>10 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 30 January 2017 | <ul style="list-style-type: none"><li>- To address regulatory concerns that subjects without clinical atherosclerotic cardiovascular disease (ASCVD) would be eligible, entry criteria were modified such that subjects without clinical ASCVD were required to have an LDL-C <math>\geq</math> 100 mg/dL.</li><li>- Modified enrollment criteria such that a subpopulation of subjects not on statin background therapy could be included</li><li>- Added a section to clarify that human immunodeficiency virus (HIV) worsening be recorded as an adverse event</li><li>- The pregnancy test schedule was revised to address regulatory agency concerns, and details were provided to clarify when serum and urine pregnancy tests were performed.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported