



## Clinical trial results:

### A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2012-001364-30       |
| Trial protocol           | BE ES DK NL PL GB DE |
| Global end of trial date | 19 November 2013     |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 20 June 2016 |
| First version publication date | 30 July 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20110116 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01763905 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Amgen Inc.  |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320                       |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 19 November 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 November 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of 12 weeks of subcutaneous (SC) evolocumab every 2 weeks (Q2W) and monthly (QM), compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

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

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

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 23 January 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 13         |
| Country: Number of subjects enrolled | United States: 99  |
| Country: Number of subjects enrolled | Belgium: 14        |
| Country: Number of subjects enrolled | Denmark: 35        |
| Country: Number of subjects enrolled | France: 14         |
| Country: Number of subjects enrolled | Germany: 15        |
| Country: Number of subjects enrolled | Netherlands: 36    |
| Country: Number of subjects enrolled | Poland: 1          |
| Country: Number of subjects enrolled | Spain: 17          |
| Country: Number of subjects enrolled | Switzerland: 7     |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Country: Number of subjects enrolled | Australia: 39      |
| Country: Number of subjects enrolled | Hong Kong: 2       |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 307 |
| EEA total number of subjects       | 147 |

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)                      | 180 |
| From 65 to 84 years                       | 127 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Men and women  $\geq 18$  to  $\leq 80$  years of age who have tried at least 2 statins and were unable to tolerate any dose or increase in statin dose due to muscle-related side effects were eligible for this study. The first participant was enrolled on 24 January 2013 and the last participant enrolled on 29 August 2013.

### Pre-assignment

Screening details:

Participants received subcutaneous placebo corresponding to the once monthly dose volume during a 6-week screening period. Those who completed the screening period and met final eligibility criteria were randomized 1:1:2:2 into 4 treatment groups. Randomization was stratified by LDL-C level ( $< 180$  mg/dL vs  $\geq 180$  mg/dL) and statin use (yes vs no).

### Period 1

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

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Ezetimibe (Q2W) |

Arm description:

Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.

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

Dosage and administration details:

10 mg administered orally once a day

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

Dosage and administration details:

Administered by subcutaneous injection

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Ezetimibe (QM) |
|------------------|----------------|

Arm description:

Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.

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

|   |  |
|---|--|
| Dosage and administration details:<br>10 mg administered orally once a day  |  |
| Investigational medicinal product name  | Placebo to Evolocumab                    |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection in pre-filled pen |
| Routes of administration  | Subcutaneous use                         |
| Dosage and administration details:<br>Administered by subcutaneous injection  |  |
| <b>Arm title</b>  | Evolocumab Q2W                           |
| Arm description:<br>Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks. |  |
| Arm type  | Experimental                             |
| Investigational medicinal product name  | Evolocumab                               |
| Investigational medicinal product code  | AMG 145                                  |
| Other name  | Repatha                                  |
| Pharmaceutical forms  | Solution for injection in pre-filled pen |
| Routes of administration  | Subcutaneous use                         |
| Dosage and administration details:<br>Administered by subcutaneous injection  |  |
| Investigational medicinal product name  | Placebo to Ezetimibe                     |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Tablet                                   |
| Routes of administration  | Oral use                                 |
| Dosage and administration details:<br>Self-administered orally once daily   |  |
| <b>Arm title</b>  | Evolocumab QM                            |
| Arm description:<br>Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.       |  |
| Arm type  | Experimental                             |
| Investigational medicinal product name  | Evolocumab                               |
| Investigational medicinal product code  | AMG 145                                  |
| Other name  | Repatha                                  |
| Pharmaceutical forms  | Solution for injection in pre-filled pen |
| Routes of administration  | Subcutaneous use                         |
| Dosage and administration details:<br>Administered by subcutaneous injection  |  |
| Investigational medicinal product name  | Placebo to Ezetimibe                     |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Tablet                                   |
| Routes of administration  | Oral use                                 |
| Dosage and administration details:<br>Self-administered orally once daily   |  |

| <b>Number of subjects in period 1</b> | Ezetimibe (Q2W) | Ezetimibe (QM) | Evolocumab Q2W |
|---------------------------------------|-----------------|----------------|----------------|
| Started                               | 51              | 51             | 103            |
| Completed                             | 45              | 50             | 94             |
| Not completed                         | 6               | 1              | 9              |
| Consent withdrawn by subject          | 1               | 1              | -              |
| Lost to follow-up                     | -               | -              | 1              |
| Decision by sponsor                   | 5               | -              | 8              |

| <b>Number of subjects in period 1</b> | Evolocumab QM |
|---------------------------------------|---------------|
| Started                               | 102           |
| Completed                             | 101           |
| Not completed                         | 1             |
| Consent withdrawn by subject          | 1             |
| Lost to follow-up                     | -             |
| Decision by sponsor                   | -             |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe (Q2W) |
|-----------------------|-----------------|

Reporting group description:

Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Ezetimibe (QM) |
|-----------------------|----------------|

Reporting group description:

Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Evolocumab Q2W |
|-----------------------|----------------|

Reporting group description:

Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.

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

Reporting group description:

Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.

| Reporting group values             | Ezetimibe (Q2W) | Ezetimibe (QM) | Evolocumab Q2W |
|------------------------------------|-----------------|----------------|----------------|
| Number of subjects                 | 51              | 51             | 103            |
| Age categorical<br>Units: Subjects |                 |                |                |

|   |        |       |       |
|---|--------|-------|-------|
| Age Continuous<br>Units: years  |        |       |       |
| arithmetic mean   | 61.7   | 60.2  | 60.5  |
| standard deviation  | ± 10.1 | ± 8.7 | ± 9.7 |
| Gender, Male/Female<br>Units: participants  |        |       |       |
| Female  | 27     | 22    | 46    |
| Male  | 24     | 29    | 57    |
| Race/Ethnicity, Customized<br>Units: Subjects   |        |       |       |
| American Indian or Alaska Native  | 0      | 0     | 0     |
| Asian   | 1      | 3     | 5     |
| Black or African American   | 0      | 1     | 3     |
| Native Hawaiian or Other Pacific Islander   | 0      | 0     | 1     |
| White   | 49     | 46    | 94    |
| Other   | 1      | 1     | 0     |
| Race/Ethnicity, Customized<br>Units: Subjects   |        |       |       |
| Hispanic or Latino  | 1      | 2     | 3     |
| Not Hispanic or Latino  | 50     | 49    | 100   |
| Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)<br>Units: Subjects |        |       |       |
| < 180 mg/dL   | 26     | 26    | 52    |
| ≥ 180 mg/dL   | 25     | 25    | 51    |

|  |               |         |         |
|--|---------------|---------|---------|
| Stratification Factor: Baseline Statin Use                         |               |         |         |
| Units: Subjects  |               |         |         |
| No   | 41            | 42      | 84      |
| Yes  | 10            | 9       | 19      |
| LDL-C Concentration  |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 194.7         | 195.2   | 192     |
| standard deviation   | ± 63.8        | ± 51.8  | ± 57    |
| Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 231.4         | 232.9   | 227.9   |
| standard deviation   | ± 66          | ± 57    | ± 56.6  |
| Apolipoprotein B Concentration                                     |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 140           | 140     | 140.2   |
| standard deviation   | ± 37          | ± 31.1  | ± 32.1  |
| Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio       |               |         |         |
| Units: ratio   |               |         |         |
| arithmetic mean  | 5.989         | 6.137   | 5.912   |
| standard deviation   | ± 2.19        | ± 1.787 | ± 1.929 |
| Apolipoprotein B/Apolipoprotein A1 Ratio                           |               |         |         |
| Units: ratio   |               |         |         |
| arithmetic mean  | 0.943         | 1.005   | 0.98    |
| standard deviation   | ± 0.282       | ± 0.294 | ± 0.318 |
| Lipoprotein(a) Concentration                                       |               |         |         |
| Units: nmol/L  |               |         |         |
| arithmetic mean  | 106.3         | 76.6    | 66.2    |
| standard deviation   | ± 101         | ± 96.7  | ± 72.5  |
| Triglyceride Concentration   |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 183.4         | 187     | 179.8   |
| standard deviation   | ± 79.8        | ± 81.5  | ± 80    |
| Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration    |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 36.7          | 37.1    | 35.2    |
| standard deviation   | ± 16          | ± 15.8  | ± 14.5  |
| High-Density Lipoprotein Cholesterol (HDL-C)                       |               |         |         |
| Units: mg/dL   |               |         |         |
| arithmetic mean  | 52.4          | 48      | 51.1    |
| standard deviation   | ± 18.3        | ± 11    | ± 16.4  |
| <b>Reporting group values</b>                                      | Evolocumab QM | Total   |         |
| Number of subjects   | 102           | 307     |         |
| Age categorical  |               |         |         |
| Units: Subjects  |               |         |         |

|   |                  |     |  |
|---|------------------|-----|--|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | 62.9<br>± 10.2   | -   |  |
| Gender, Male/Female<br>Units: participants  |                  |     |  |
| Female  | 46               | 141 |  |
| Male  | 56               | 166 |  |
| Race/Ethnicity, Customized<br>Units: Subjects   |                  |     |  |
| American Indian or Alaska Native  | 0                | 0   |  |
| Asian   | 1                | 10  |  |
| Black or African American   | 3                | 7   |  |
| Native Hawaiian or Other Pacific Islander   | 0                | 1   |  |
| White   | 98               | 287 |  |
| Other   | 0                | 2   |  |
| Race/Ethnicity, Customized<br>Units: Subjects   |                  |     |  |
| Hispanic or Latino  | 1                | 7   |  |
| Not Hispanic or Latino  | 101              | 300 |  |
| Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)<br>Units: Subjects                                       |                  |     |  |
| < 180 mg/dL   | 52               | 156 |  |
| ≥ 180 mg/dL   | 50               | 151 |  |
| Stratification Factor: Baseline Statin Use<br>Units: Subjects   |                  |     |  |
| No  | 82               | 249 |  |
| Yes   | 20               | 58  |  |
| LDL-C Concentration<br>Units: mg/dL<br>arithmetic mean<br>standard deviation  | 192.2<br>± 61.2  | -   |  |
| Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration<br>Units: mg/dL<br>arithmetic mean<br>standard deviation | 222.1<br>± 63.2  | -   |  |
| Apolipoprotein B Concentration<br>Units: mg/dL<br>arithmetic mean<br>standard deviation                                     | 133.1<br>± 32.2  | -   |  |
| Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio<br>Units: ratio<br>arithmetic mean<br>standard deviation       | 5.506<br>± 1.925 | -   |  |
| Apolipoprotein B/Apolipoprotein A1 Ratio<br>Units: ratio<br>arithmetic mean<br>standard deviation                           | 0.901<br>± 0.283 | -   |  |

|  |                 |   |  |
|--|-----------------|---|--|
| Lipoprotein(a) Concentration<br>Units: nmol/L<br>arithmetic mean<br>standard deviation                                   | 70.9<br>± 99.9  | - |  |
| Triglyceride Concentration<br>Units: mg/dL<br>arithmetic mean<br>standard deviation                                      | 149.3<br>± 63.1 | - |  |
| Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration<br>Units: mg/dL<br>arithmetic mean<br>standard deviation | 29.9<br>± 12.6  | - |  |
| High-Density Lipoprotein Cholesterol (HDL-C)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation                    | 54<br>± 16      | - |  |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | Ezetimibe (Q2W) |
| Reporting group description:<br>Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.       |                 |
| Reporting group title   | Ezetimibe (QM)  |
| Reporting group description:<br>Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.             |                 |
| Reporting group title   | Evolocumab Q2W  |
| Reporting group description:<br>Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks. |                 |
| Reporting group title   | Evolocumab QM   |
| Reporting group description:<br>Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.       |                 |

### Primary: Percent Change From Baseline in LDL-C at Week 12

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in LDL-C at Week 12 |
| End point description:<br>Calculated LDL-C was determined based on the Friedewald equation. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline and Week 12  |  |

| End point values                    | Ezetimibe (Q2W)      | Ezetimibe (QM)       | Evolocumab Q2W       | Evolocumab QM       |
|-------------------------------------|----------------------|----------------------|----------------------|---------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group     |
| Number of subjects analysed         | 51                   | 51                   | 103                  | 102                 |
| Units: percent change               |                      |                      |                      |                     |
| least squares mean (standard error) | -18.08 ( $\pm$ 2.52) | -15.05 ( $\pm$ 2.13) | -56.14 ( $\pm$ 1.91) | -52.6 ( $\pm$ 1.58) |

### Statistical analyses

|  |                                   |
|--|-----------------------------------|
| Statistical analysis title   | Evolocumab Q2W vs Ezetimibe (Q2W) |
| Statistical analysis description:<br>The null hypothesis was that there is no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist. |                                   |
| Comparison groups  | Evolocumab Q2W v Ezetimibe (Q2W)  |

|   |  |
|---|--|
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[1]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -38.06                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -43.73                                 |
| upper limit                             | -32.99                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.87                                   |

Notes:

[1] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Evolocumab QM vs Ezetimibe (QM) |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The null hypothesis was that there is no mean difference in the percent change from baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

|   |  |
|---|--|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[2]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -37.55                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -42.16                                 |
| upper limit                             | -32.94                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.33                                   |

Notes:

[2] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Primary: Mean Percent Change From Baseline in LDL-C at Weeks 10 and 12**

|                 |   |
|-----------------|---|
| End point title | Mean Percent Change From Baseline in LDL-C at Weeks 10 and 12 |
|-----------------|---|

End point description:

Calculated LDL-C was determined based on the Friedewald equation.

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

End point timeframe:

Baseline and Weeks 10 and 12

| <b>End point values</b>             | Ezetimibe (Q2W)     | Ezetimibe (QM)       | Evolocumab Q2W       | Evolocumab QM        |
|-------------------------------------|---------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group     | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 51                  | 51                   | 103                  | 102                  |
| Units: percent change               |                     |                      |                      |                      |
| least squares mean (standard error) | -19.21 ( $\pm$ 2.4) | -16.62 ( $\pm$ 2.03) | -56.11 ( $\pm$ 1.83) | -55.31 ( $\pm$ 1.53) |

## Statistical analyses

| <b>Statistical analysis title</b> | Evolocumab Q2W vs Ezetimibe (Q2W) |
|-----------------------------------|-----------------------------------|
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The null hypothesis was that there is no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

|   |  |
|---|--|
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[3]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -36.9                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -42.26                                 |
| upper limit                             | -31.55                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.71                                   |

Notes:

[3] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

| <b>Statistical analysis title</b> | Evolocumab QM vs Ezetimibe (QM) |
|-----------------------------------|---------------------------------|
|-----------------------------------|---------------------------------|

Statistical analysis description:

The null hypothesis was that there is no mean difference in the percent change from baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

|   |  |
|---|--|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[4]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -38.69                                 |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -43.06                     |
| upper limit          | -34.22                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.21                       |

Notes:

[4] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Mean Change From Baseline in LDL-C at Weeks 10 and 12

|   |   |
|---|---|
| End point title   | Mean Change From Baseline in LDL-C at Weeks 10 and 12 |
| End point description:<br>Calculated LDL-C was determined based on the Friedewald equation. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline and Weeks 10 and 12  |   |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: mg/dL                        |                 |                 |                 |                 |
| least squares mean (standard error) | -39.1 (± 5.1)   | -33 (± 4.5)     | -105.4 (± 3.9)  | -103.6 (± 3.4)  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[5]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -70.6                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -80.5                                  |
| upper limit                             | -60.7                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 5                                      |

Notes:

[5] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[6]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -66.3                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -77.9                                  |
| upper limit                             | -54.7                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 5.9                                    |

Notes:

[6] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Change From Baseline in LDL-C at Week 12

|   |  |
|---|--|
| End point title   | Change From Baseline in LDL-C at Week 12 |
| End point description:  |  |
| Calculated LDL-C was determined based on the Friedewald equation. |  |
| End point type  | Secondary                                |
| End point timeframe:  |  |
| Baseline and Week 12  |  |

| <b>End point values</b>             | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: mg/dL                        |                 |                 |                 |                 |
| least squares mean (standard error) | -36.2 (± 5.4)   | -30.2 (± 4.7)   | -106 (± 4.1)    | -99 (± 3.5)     |

### Statistical analyses

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Evolocumab QM vs Ezetimibe (QM) |
| Comparison groups                 | Ezetimibe (QM) v Evolocumab QM  |

|   |  |
|---|--|
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[7]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -68.8                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -79.2                                  |
| upper limit                             | -58.4                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 5.3                                    |

Notes:

[7] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[8]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -69.7                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -82                                    |
| upper limit                             | -57.5                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 6.2                                    |

Notes:

[8] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Mean Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Weeks 10 and 12**

|   |   |
|---|---|
| End point title   | Mean Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Weeks 10 and 12 |
| End point description:  |   |
| Mean low density lipoprotein-cholesterol response at Weeks 10 and 12 (low density lipoprotein-cholesterol < 70 mg/dL [1.8 mmol/L]). |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Weeks 10 and 12   |   |

| <b>End point values</b>           | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W      | Evolocumab QM     |
|-----------------------------------|-----------------|-----------------|---------------------|-------------------|
| Subject group type                | Reporting group | Reporting group | Reporting group     | Reporting group   |
| Number of subjects analysed       | 51              | 51              | 103                 | 102               |
| Units: percentage of participants |                 |                 |                     |                   |
| number (confidence interval 95%)  | 2 (0.4 to 10.5) | 0 (0 to 7.3)    | 45.5 (36.2 to 55.2) | 42 (32.8 to 51.8) |

### Statistical analyses

| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W) |
|---|-----------------------------------|
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W  |
| Number of subjects included in analysis | 154                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | < 0.001 <sup>[9]</sup>            |
| Method                                  | Cochran-Mantel-Haenszel           |
| Parameter estimate                      | Treatment Difference              |
| Point estimate                          | 43.5                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 30.9                              |
| upper limit                             | 53.4                              |

Notes:

[9] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM) |
|---|---------------------------------|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM  |
| Number of subjects included in analysis | 153                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | < 0.001 <sup>[10]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel         |
| Parameter estimate                      | Treatment Difference            |
| Point estimate                          | 42                              |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 30.3                            |
| upper limit                             | 51.8                            |

Notes:

[10] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Week 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Week 12 |
|-----------------|--|

End point description:

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 12              |           |

| <b>End point values</b>           | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W    | Evolocumab QM       |
|-----------------------------------|-----------------|-----------------|-------------------|---------------------|
| Subject group type                | Reporting group | Reporting group | Reporting group   | Reporting group     |
| Number of subjects analysed       | 51              | 51              | 103               | 102                 |
| Units: percentage of participants |                 |                 |                   |                     |
| number (confidence interval 95%)  | 2 (0.4 to 10.7) | 0 (0 to 7.9)    | 50 (40.3 to 59.7) | 37.5 (28.5 to 47.5) |

### Statistical analyses

|   |                                   |
|---|-----------------------------------|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W) |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W  |
| Number of subjects included in analysis | 154                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | < 0.001 <sup>[11]</sup>           |
| Method                                  | Cochran-Mantel-Haenszel           |
| Parameter estimate                      | Treatment Difference              |
| Point estimate                          | 48                                |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 35                                |
| upper limit                             | 57.8                              |

Notes:

[11] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM) |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM  |
| Number of subjects included in analysis | 153                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | < 0.001 <sup>[12]</sup>         |
| Method                                  | Cochran-Mantel-Haenszel         |
| Parameter estimate                      | Treatment Difference            |
| Point estimate                          | 37.5                            |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 25.5    |
| upper limit         | 47.5    |

Notes:

[12] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and statin use. For testing, non-achievement was imputed for participants with missing data. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05

### Secondary: Mean Percent Change From Baseline in Non-HDL-C at Weeks 10 and 12

|                 |   |
|-----------------|---|
| End point title | Mean Percent Change From Baseline in Non-HDL-C at Weeks 10 and 12 |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline and Weeks 10 and 12

| End point values                    | Ezetimibe (Q2W)      | Ezetimibe (QM)       | Evolocumab Q2W       | Evolocumab QM       |
|-------------------------------------|----------------------|----------------------|----------------------|---------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group     |
| Number of subjects analysed         | 51                   | 51                   | 103                  | 102                 |
| Units: percent change               |                      |                      |                      |                     |
| least squares mean (standard error) | -17.18 ( $\pm$ 2.15) | -14.54 ( $\pm$ 1.86) | -48.72 ( $\pm$ 1.64) | -49.13 ( $\pm$ 1.4) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[13]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -31.53                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -36.34                                 |
| upper limit                             | -26.73                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.43                                   |

Notes:

[13] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[14]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -34.58                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -38.63                                 |
| upper limit                             | -30.54                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.05                                   |

Notes:

[14] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Percent Change from Baseline in Non-HDL-C at Week 12

|                        |  |
|------------------------|--|
| End point title        | Percent Change from Baseline in Non-HDL-C at Week 12 |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline and Week 12   |  |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -16.53 (± 2.3)  | -13.16 (± 1.93) | -48.62 (± 1.74) | -46.15 (± 1.43) |

### Statistical analyses

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Evolocumab Q2W vs Ezetimibe (Q2W) |
| Comparison groups                 | Ezetimibe (Q2W) v Evolocumab Q2W  |

|   |  |
|---|--|
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[15]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -32.09                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -37.28                                 |
| upper limit                             | -26.9                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.63                                   |

Notes:

[15] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[16]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -32.99                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -37.19                                 |
| upper limit                             | -28.79                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.12                                   |

Notes:

[16] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Mean Percent Change From Baseline in Apolipoprotein B at Weeks 10 and 12**

|                              |  |
|------------------------------|--|
| End point title              | Mean Percent Change From Baseline in Apolipoprotein B at Weeks 10 and 12 |
| End point description:       |  |
| End point type               | Secondary  |
| End point timeframe:         |  |
| Baseline and Weeks 10 and 12 |  |

| <b>End point values</b>             | Ezetimibe (Q2W)      | Ezetimibe (QM)       | Evolocumab Q2W       | Evolocumab QM        |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 51                   | 51                   | 103                  | 102                  |
| Units: percent change               |                      |                      |                      |                      |
| least squares mean (standard error) | -13.67 ( $\pm$ 2.15) | -11.02 ( $\pm$ 2.21) | -45.88 ( $\pm$ 1.68) | -46.01 ( $\pm$ 1.65) |

## Statistical analyses

| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
|---|--|
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[17]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -32.2                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -36.92                                 |
| upper limit                             | -27.49                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.39                                   |

Notes:

[17] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
|---|--|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[18]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -34.99                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -39.59                                 |
| upper limit                             | -30.39                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.33                                   |

Notes:

[18] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

## Secondary: Percent Change From Baseline in Apolipoprotein B at Week 12

End point title Percent Change From Baseline in Apolipoprotein B at Week 12

End point description:

End point type Secondary

End point timeframe:

Baseline and Week 12

| End point values                    | Ezetimibe (Q2W)      | Ezetimibe (QM)      | Evolocumab Q2W       | Evolocumab QM        |
|-------------------------------------|----------------------|---------------------|----------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group     | Reporting group      | Reporting group      |
| Number of subjects analysed         | 51                   | 51                  | 103                  | 102                  |
| Units: percent change               |                      |                     |                      |                      |
| least squares mean (standard error) | -12.95 ( $\pm$ 2.32) | -9.97 ( $\pm$ 2.34) | -45.81 ( $\pm$ 1.79) | -43.07 ( $\pm$ 1.73) |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[19]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -32.86                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -38.04                                 |
| upper limit                             | -27.68                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.62                                   |

Notes:

[19] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| Statistical analysis title              | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[20]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -33.1                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -38.04                     |
| upper limit          | -28.17                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.5                        |

Notes:

[20] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Mean Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Weeks 10 and 12

|                 |  |
|-----------------|--|
| End point title | Mean Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Weeks 10 and 12 |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline and Weeks 10 and 12

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -13.44 (± 2.14) | -11.2 (± 2.16)  | -40.83 (± 1.65) | -41.14 (± 1.62) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[21]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -27.39                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -32.11                                 |
| upper limit                             | -22.67                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.39                                   |

Notes:

[21] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[22]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -29.94                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -34.72                                 |
| upper limit                             | -25.17                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.42                                   |

Notes:

[22] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Week 12**

|                        |   |
|------------------------|---|
| End point title        | Percent Change From Baseline in the Total Cholesterol/High Density Lipoprotein Cholesterol Ratio at Week 12 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline and Week 12   |   |

| <b>End point values</b>             | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -14.13 (± 2.3)  | -9.92 (± 2.34)  | -40.42 (± 1.75) | -38.57 (± 1.73) |

### **Statistical analyses**

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Evolocumab Q2W vs Ezetimibe (Q2W) |
| Comparison groups                 | Ezetimibe (Q2W) v Evolocumab Q2W  |

|   |  |
|---|--|
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[23]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -26.28                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -31.42                                 |
| upper limit                             | -21.15                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.6                                    |

Notes:

[23] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[24]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -28.66                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -33.88                                 |
| upper limit                             | -23.43                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.64                                   |

Notes:

[24] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12**

|                 |  |
|-----------------|--|
| End point title | Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12 |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline and Weeks 10 and 12

| <b>End point values</b>             | Ezetimibe (Q2W)   | Ezetimibe (QM)       | Evolocumab Q2W       | Evolocumab QM        |
|-------------------------------------|-------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group   | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 51                | 51                   | 103                  | 102                  |
| Units: percent change               |                   |                      |                      |                      |
| least squares mean (standard error) | -13 ( $\pm$ 2.27) | -11.94 ( $\pm$ 2.56) | -47.86 ( $\pm$ 1.77) | -48.31 ( $\pm$ 1.92) |

## Statistical analyses

| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
|---|--|
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[25]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -34.86                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -39.84                                 |
| upper limit                             | -29.88                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.52                                   |

Notes:

[25] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
|---|--|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[26]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -36.37                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -41.73                                 |
| upper limit                             | -31.01                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.71                                   |

Notes:

[26] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

## Secondary: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12

|  |   |
|--|---|
| End point title                              | Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12 |
| End point description:                       |   |
| End point type                               | Secondary   |
| End point timeframe:<br>Baseline and Week 12 |   |

| End point values                    | Ezetimibe (Q2W)      | Ezetimibe (QM)       | Evolocumab Q2W      | Evolocumab QM        |
|-------------------------------------|----------------------|----------------------|---------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group     | Reporting group      |
| Number of subjects analysed         | 51                   | 51                   | 103                 | 102                  |
| Units: percent change               |                      |                      |                     |                      |
| least squares mean (standard error) | -13.14 ( $\pm$ 2.47) | -11.37 ( $\pm$ 2.71) | -47.66 ( $\pm$ 1.9) | -45.51 ( $\pm$ 2.01) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[27]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -34.53                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -40.05                                 |
| upper limit                             | -29                                    |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.79                                   |

Notes:

[27] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Evolocumab QM vs Ezetimibe (QM) |
| Comparison groups                 | Ezetimibe (QM) v Evolocumab QM  |

|   |  |
|---|--|
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[28]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -34.13                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -39.87                                 |
| upper limit                             | -28.39                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.91                                   |

Notes:

[28] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Mean Percent Change From Baseline in Lipoprotein (a) at Weeks 10 and 12

|  |   |
|--|---|
| End point title                                      | Mean Percent Change From Baseline in Lipoprotein (a) at Weeks 10 and 12 |
| End point description:                               |   |
| End point type                                       | Secondary   |
| End point timeframe:<br>Baseline and Weeks 10 and 12 |   |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -2.3 (± 3.36)   | 1.55 (± 4.01)   | -26.2 (± 2.64)  | -23.72 (± 2.97) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[29]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -25.26                                 |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -33.75                     |
| upper limit          | -16.77                     |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 4.3                        |

Notes:

[29] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[30]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -23.9                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -31.27                                 |
| upper limit                             | -16.54                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 3.73                                   |

Notes:

[30] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

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

|                        |  |
|------------------------|--|
| End point title        | Percent Change From Baseline in Lipoprotein (a) at Week 12 |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline and Week 12   |  |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -1.74 (± 3.58)  | 5.81 (± 5.1)    | -27.03 (± 2.78) | -22.07 (± 3.66) |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[31]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -25.29                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -33.26                                 |
| upper limit                             | -17.33                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 4.03                                   |

Notes:

[31] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | < 0.001 <sup>[32]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -27.88                                 |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -39.21                                 |
| upper limit                             | -16.56                                 |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 5.73                                   |

Notes:

[32] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

## Secondary: Mean Percent Change From Baseline in Triglycerides at Weeks 10 and 12

|                 |   |
|-----------------|---|
| End point title | Mean Percent Change From Baseline in Triglycerides at Weeks 10 and 12 |
|-----------------|---|

End point description:

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Baseline and Weeks 10 and 12 |           |

| <b>End point values</b>             | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -3.74 (± 3.88)  | -0.32 (± 4.65)  | -6.32 (± 2.94)  | -6.73 (± 3.44)  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.97 <sup>[33]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -2.59                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -11.38                                 |
| upper limit                             | 6.2                                    |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 4.45                                   |

Notes:

[33] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Ezetimibe (QM) v Evolocumab QM         |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.33 <sup>[34]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -6.42                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -16.55                     |
| upper limit          | 3.71                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 5.13                       |

Notes:

[34] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Percent Change From Baseline in Triglycerides at Week 12

|  |  |
|--|--|
| End point title                              | Percent Change From Baseline in Triglycerides at Week 12 |
| End point description:                       |  |
| End point type                               | Secondary  |
| End point timeframe:<br>Baseline and Week 12 |  |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -5.47 (± 4.25)  | 2.16 (± 5.52)   | -3.88 (± 3.18)  | -2.53 (± 3.98)  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.97 <sup>[35]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 1.58                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -8.14                                  |
| upper limit                             | 11.31                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 4.92                                   |

Notes:

[35] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.33 [36]                            |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -4.69                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -17.04                                 |
| upper limit                             | 7.67                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 6.25                                   |

Notes:

[36] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Mean Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 10 and 12**

|                              |  |
|------------------------------|--|
| End point title              | Mean Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Weeks 10 and 12 |
| End point description:       |  |
| End point type               | Secondary  |
| End point timeframe:         |  |
| Baseline and Weeks 10 and 12 |  |

| <b>End point values</b>             | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | 0.33 (± 1.98)   | 1.44 (± 2.03)   | 5.48 (± 1.51)   | 7.18 (± 1.51)   |

### **Statistical analyses**

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Evolocumab Q2W vs Ezetimibe (Q2W) |
| Comparison groups                 | Ezetimibe (Q2W) v Evolocumab Q2W  |

|   |  |
|---|--|
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.068 <sup>[37]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 5.15                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 0.74                                   |
| upper limit                             | 9.56                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.23                                   |

Notes:

[37] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.13 <sup>[38]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 5.74                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 1.23                                   |
| upper limit                             | 10.24                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.28                                   |

Notes:

[38] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### **Secondary: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 12**

|  |   |
|--|---|
| End point title                              | Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 12 |
| End point description:                       |   |
| End point type                               | Secondary   |
| End point timeframe:<br>Baseline and Week 12 |   |

| <b>End point values</b>             | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | 1.77 (± 2.22)   | 1.64 (± 2.22)   | 5.34 (± 1.67)   | 6.47 (± 1.63)   |

## Statistical analyses

| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
|---|--|
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.068 <sup>[39]</sup>                |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 3.57                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -1.49                                  |
| upper limit                             | 8.63                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.56                                   |

Notes:

[39] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
|---|--|
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.13 <sup>[40]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 4.83                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -0.16                                  |
| upper limit                             | 9.81                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 2.52                                   |

Notes:

[40] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

## Secondary: Mean Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Weeks 10 and 12

|                              |  |
|------------------------------|--|
| End point title              | Mean Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Weeks 10 and 12 |
| End point description:       |  |
| End point type               | Secondary  |
| End point timeframe:         |  |
| Baseline and Weeks 10 and 12 |  |

| End point values                    | Ezetimibe (Q2W)    | Ezetimibe (QM)      | Evolocumab Q2W     | Evolocumab QM       |
|-------------------------------------|--------------------|---------------------|--------------------|---------------------|
| Subject group type                  | Reporting group    | Reporting group     | Reporting group    | Reporting group     |
| Number of subjects analysed         | 51                 | 51                  | 103                | 102                 |
| Units: percent change               |                    |                     |                    |                     |
| least squares mean (standard error) | -5.76 ( $\pm$ 3.8) | -2.93 ( $\pm$ 4.41) | -7.6 ( $\pm$ 2.89) | -6.46 ( $\pm$ 3.21) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.97 <sup>[41]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -1.84                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -10.43                                 |
| upper limit                             | 6.75                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 4.35                                   |

Notes:

[41] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Evolocumab QM vs Ezetimibe (QM) |
| Comparison groups                 | Ezetimibe (QM) v Evolocumab QM  |

|   |  |
|---|--|
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.33 <sup>[42]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -3.53                                  |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -13.12                                 |
| upper limit                             | 6.06                                   |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 4.85                                   |

Notes:

[42] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

### Secondary: Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Week 12

|  |   |
|--|---|
| End point title                              | Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol at Week 12 |
| End point description:                       |   |
| End point type                               | Secondary   |
| End point timeframe:<br>Baseline and Week 12 |   |

| End point values                    | Ezetimibe (Q2W) | Ezetimibe (QM)  | Evolocumab Q2W  | Evolocumab QM   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 51              | 51              | 103             | 102             |
| Units: percent change               |                 |                 |                 |                 |
| least squares mean (standard error) | -5.49 (± 4.05)  | -2.25 (± 5.11)  | -6.16 (± 3.08)  | -2.18 (± 3.6)   |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab Q2W vs Ezetimibe (Q2W)      |
| Comparison groups                       | Ezetimibe (Q2W) v Evolocumab Q2W       |
| Number of subjects included in analysis | 154                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.97 <sup>[43]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | -0.67                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -9.96                      |
| upper limit          | 8.61                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 4.7                        |

Notes:

[43] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Evolocumab QM vs Ezetimibe (QM)        |
| Comparison groups                       | Ezetimibe (QM) v Evolocumab QM         |
| Number of subjects included in analysis | 153                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.33 <sup>[44]</sup>                 |
| Method                                  | Repeated measures linear effects model |
| Parameter estimate                      | LS Mean Treatment Difference           |
| Point estimate                          | 0.08                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -11.24                                 |
| upper limit                             | 11.39                                  |
| Variability estimate                    | Standard error of the mean             |
| Dispersion value                        | 5.72                                   |

Notes:

[44] - The model includes treatment group, baseline LDL-C level and statin use, scheduled visit, and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 28 days after the last dose (12 weeks).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe (Q2W) |
|-----------------------|-----------------|

Reporting group description:

Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Ezetimibe (QM) |
|-----------------------|----------------|

Reporting group description:

Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Evolocumab Q2W |
|-----------------------|----------------|

Reporting group description:

Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.

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

Reporting group description:

Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.

| <b>Serious adverse events</b>                                       | Ezetimibe (Q2W) | Ezetimibe (QM) | Evolocumab Q2W  |
|---|-----------------|----------------|-----------------|
| Total subjects affected by serious adverse events                   |                 |                |                 |
| subjects affected / exposed   | 1 / 51 (1.96%)  | 3 / 51 (5.88%) | 5 / 103 (4.85%) |
| number of deaths (all causes)                                       | 0               | 0              | 0               |
| number of deaths resulting from adverse events                      |                 |                |                 |
| Investigations  |                 |                |                 |
| Hepatic enzyme increased  |                 |                |                 |
| subjects affected / exposed   | 0 / 51 (0.00%)  | 0 / 51 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |                 |
| Bladder transitional cell carcinoma stage III                       |                 |                |                 |
| subjects affected / exposed   | 0 / 51 (0.00%)  | 0 / 51 (0.00%) | 1 / 103 (0.97%) |
| 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 / 51 (0.00%) | 0 / 51 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Neuroendocrine carcinoma metastatic             |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 0 / 51 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Surgical and medical procedures                 |                |                |                 |
| Cartilage graft                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 0 / 51 (0.00%) | 0 / 103 (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           |
| Osteotomy                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 0 / 51 (0.00%) | 0 / 103 (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           |
| Spinal decompression                            |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 1 / 51 (1.96%) | 0 / 103 (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           |
| Gastrointestinal disorders                      |                |                |                 |
| Gastrointestinal motility disorder              |                |                |                 |
| subjects affected / exposed                     | 1 / 51 (1.96%) | 0 / 51 (0.00%) | 0 / 103 (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           |
| Inguinal hernia                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 1 / 51 (1.96%) | 0 / 103 (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 and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 51 (0.00%) | 0 / 51 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Infections and infestations</b>              |                |                |                 |
| Kidney infection                                |                |                |                 |
| subjects affected / exposed                     | 0 / 51 (0.00%) | 1 / 51 (1.96%) | 0 / 103 (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           |

|  |                 |  |  |
|--|-----------------|--|--|
| <b>Serious adverse events</b>  | Evolocumab QM   |  |  |
| <b>Total subjects affected by serious adverse events</b>                   |                 |  |  |
| subjects affected / exposed  | 1 / 102 (0.98%) |  |  |
| number of deaths (all causes)  | 0               |  |  |
| number of deaths resulting from adverse events                             |                 |  |  |
| <b>Investigations</b>  |                 |  |  |
| Hepatic enzyme increased   |                 |  |  |
| subjects affected / exposed  | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all                            | 0 / 0           |  |  |
| deaths causally related to treatment / all                                 | 0 / 0           |  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                 |  |  |
| Bladder transitional cell carcinoma stage III                              |                 |  |  |
| subjects affected / exposed  | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all                            | 0 / 0           |  |  |
| deaths causally related to treatment / all                                 | 0 / 0           |  |  |
| Lipoma   |                 |  |  |
| subjects affected / exposed  | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all                            | 0 / 0           |  |  |
| deaths causally related to treatment / all                                 | 0 / 0           |  |  |
| Neuroendocrine carcinoma metastatic  |                 |  |  |
| subjects affected / exposed  | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all                            | 0 / 0           |  |  |
| deaths causally related to treatment / all                                 | 0 / 0           |  |  |
| <b>Surgical and medical procedures</b>                                     |                 |  |  |
| Cartilage graft  |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Osteotomy</b>                                       |                 |  |  |
| subjects affected / exposed                            | 1 / 102 (0.98%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Spinal decompression</b>                            |                 |  |  |
| subjects affected / exposed                            | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Gastrointestinal disorders</b>                      |                 |  |  |
| <b>Gastrointestinal motility disorder</b>              |                 |  |  |
| subjects affected / exposed                            | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Inguinal hernia</b>                                 |                 |  |  |
| subjects affected / exposed                            | 0 / 102 (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> |                 |  |  |
| <b>Back pain</b>                                       |                 |  |  |
| subjects affected / exposed                            | 0 / 102 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| <b>Kidney infection</b>                                |                 |  |  |
| subjects affected / exposed                            | 0 / 102 (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: 5 %

| <b>Non-serious adverse events</b>  | Ezetimibe (Q2W)  | Ezetimibe (QM)   | Evolocumab Q2W    |
|--|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 20 / 51 (39.22%) | 29 / 51 (56.86%) | 28 / 103 (27.18%) |
| Nervous system disorders   |                  |                  |                   |
| Headache   |                  |                  |                   |
| subjects affected / exposed  | 3 / 51 (5.88%)   | 6 / 51 (11.76%)  | 4 / 103 (3.88%)   |
| occurrences (all)  | 3                | 9                | 7                 |
| Paraesthesia   |                  |                  |                   |
| subjects affected / exposed  | 1 / 51 (1.96%)   | 4 / 51 (7.84%)   | 0 / 103 (0.00%)   |
| occurrences (all)  | 1                | 4                | 0                 |
| General disorders and administration site conditions                                 |                  |                  |                   |
| Fatigue  |                  |                  |                   |
| subjects affected / exposed  | 4 / 51 (7.84%)   | 6 / 51 (11.76%)  | 3 / 103 (2.91%)   |
| occurrences (all)  | 4                | 7                | 3                 |
| Injection site erythema  |                  |                  |                   |
| subjects affected / exposed  | 0 / 51 (0.00%)   | 3 / 51 (5.88%)   | 2 / 103 (1.94%)   |
| occurrences (all)  | 0                | 3                | 2                 |
| Gastrointestinal disorders   |                  |                  |                   |
| Diarrhoea  |                  |                  |                   |
| subjects affected / exposed  | 3 / 51 (5.88%)   | 4 / 51 (7.84%)   | 3 / 103 (2.91%)   |
| occurrences (all)  | 3                | 4                | 4                 |
| Nausea   |                  |                  |                   |
| subjects affected / exposed  | 2 / 51 (3.92%)   | 5 / 51 (9.80%)   | 3 / 103 (2.91%)   |
| occurrences (all)  | 2                | 5                | 4                 |
| Skin and subcutaneous tissue disorders   |                  |                  |                   |
| Pruritus   |                  |                  |                   |
| subjects affected / exposed  | 1 / 51 (1.96%)   | 3 / 51 (5.88%)   | 0 / 103 (0.00%)   |
| occurrences (all)  | 1                | 3                | 0                 |
| Musculoskeletal and connective tissue disorders                                      |                  |                  |                   |
| Muscle spasms  |                  |                  |                   |
| subjects affected / exposed  | 3 / 51 (5.88%)   | 1 / 51 (1.96%)   | 5 / 103 (4.85%)   |
| occurrences (all)  | 6                | 1                | 7                 |
| Myalgia  |                  |                  |                   |
| subjects affected / exposed  | 7 / 51 (13.73%)  | 11 / 51 (21.57%) | 7 / 103 (6.80%)   |
| occurrences (all)  | 7                | 15               | 10                |
| Pain in extremity  |                  |                  |                   |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 51 (0.00%)<br>0 | 1 / 51 (1.96%)<br>1 | 2 / 103 (1.94%)<br>2 |
| Infections and infestations                      |                     |                     |                      |
| Influenza  |                     |                     |                      |
| subjects affected / exposed<br>occurrences (all) | 3 / 51 (5.88%)<br>4 | 0 / 51 (0.00%)<br>0 | 1 / 103 (0.97%)<br>1 |
| Nasopharyngitis                                  |                     |                     |                      |
| subjects affected / exposed<br>occurrences (all) | 3 / 51 (5.88%)<br>3 | 0 / 51 (0.00%)<br>0 | 5 / 103 (4.85%)<br>5 |

|   |                         |  |  |
|---|-------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Evolocumab QM           |  |  |
| Total subjects affected by non-serious adverse events |                         |  |  |
| subjects affected / exposed                           | 42 / 102 (41.18%)       |  |  |
| Nervous system disorders                              |                         |  |  |
| Headache  |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 12 / 102 (11.76%)<br>12 |  |  |
| Paraesthesia  |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 2 / 102 (1.96%)<br>2    |  |  |
| General disorders and administration site conditions  |                         |  |  |
| Fatigue   |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 6 / 102 (5.88%)<br>6    |  |  |
| Injection site erythema                               |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 2 / 102 (1.96%)<br>2    |  |  |
| Gastrointestinal disorders                            |                         |  |  |
| Diarrhoea   |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 2 / 102 (1.96%)<br>2    |  |  |
| Nausea  |                         |  |  |
| subjects affected / exposed<br>occurrences (all)      | 6 / 102 (5.88%)<br>9    |  |  |
| Skin and subcutaneous tissue disorders                |                         |  |  |
| Pruritus  |                         |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 102 (0.00%)<br>0 |  |  |
| Musculoskeletal and connective tissue disorders  |                      |  |  |
| Muscle spasms                                    |                      |  |  |
| subjects affected / exposed                      | 8 / 102 (7.84%)      |  |  |
| occurrences (all)                                | 9                    |  |  |
| Myalgia  |                      |  |  |
| subjects affected / exposed                      | 9 / 102 (8.82%)      |  |  |
| occurrences (all)                                | 12                   |  |  |
| Pain in extremity                                |                      |  |  |
| subjects affected / exposed                      | 12 / 102 (11.76%)    |  |  |
| occurrences (all)                                | 19                   |  |  |
| Infections and infestations                      |                      |  |  |
| Influenza  |                      |  |  |
| subjects affected / exposed                      | 0 / 102 (0.00%)      |  |  |
| occurrences (all)                                | 0                    |  |  |
| Nasopharyngitis                                  |                      |  |  |
| subjects affected / exposed                      | 2 / 102 (1.96%)      |  |  |
| occurrences (all)                                | 2                    |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 01 August 2012   | <ul style="list-style-type: none"><li>- added testing for prior or existing HCV infection in high risk individuals and evaluation of viral load in those who show evidence thereof</li><li>- strengthened the definition of statin-intolerance by requiring subjects to have failed 2 statins instead of 1</li><li>- clarified that subjects with a known sensitivity to the "active substances or their excipients" were excluded</li><li>- added urine pregnancy testing at day 1, week 4, and week 8 for women of childbearing potential</li><li>- implemented minor clarifications and error corrections</li></ul>   |
| 10 October 2012  | <ul style="list-style-type: none"><li>- added the GAUSS-2 study acronym and short title</li><li>- made minor modification of LDL-C inclusion limits in accordance with NCEP ATP III risk categories</li><li>- added new evolocumab formulation and autoinjectors to allow administration of investigational product in a home-use setting</li><li>- revised schedule of assessment and description of procedures in Section 7 to replace weeks 4 and 6 visits with home-use IP administration</li><li>- added reporting requirements for product/device complaints</li><li>- updated program status in evolocumab background section</li><li>- provided instruction regarding missed ezetimibe doses</li><li>- added subjects with a history of HCV infection to the ones at high risk of HCV infection to the HCV antibody testing and viral load monitoring, if positive</li><li>- updated sections on collection and reporting of adverse events and serious adverse events, including adding device-related adverse events, and the eSAE contingency form</li><li>- moved change from baseline in VLDL-C at week 12 from tertiary to secondary endpoints</li><li>- added transient ischemic attacks and non-coronary revascularization as exploratory endpoints</li><li>- implemented minor clarifications and error corrections</li></ul> |
| 10 December 2012 | <ul style="list-style-type: none"><li>- added the LDL-C endpoint of mean percent change from baseline at weeks 10 and 12 as a co-primary endpoint</li><li>- added the means of weeks 10 and 12 as co-secondary endpoints to all secondary endpoints for the same reason as above</li><li>- added alert threshold for elevated triglycerides</li><li>- added publication references for primary result publications of phase 2 studies MENDEL and LAPLACE</li><li>- introduced the simplified terminology of once monthly (QM) dosing</li><li>- implemented minor clarifications and error corrections</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported