



## Clinical trial results:

### A Randomized, Double-Blind, Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of SAR236553/REGN727 over 24 weeks in Patients with Hypercholesterolemia

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-001424-38 |
| Trial protocol           | BE FI NL       |
| Global end of trial date | 09 July 2013   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 01 April 2016  |
| First version publication date | 06 August 2015 |

#### Trial information

##### Trial identification

|                       |                     |
|-----------------------|---------------------|
| Sponsor protocol code | A poster - EFC11716 |
|-----------------------|---------------------|

##### Additional study identifiers

|                                    |                          |
|------------------------------------|--------------------------|
| ISRCTN number                      | -                        |
| ClinicalTrials.gov id (NCT number) | NCT01644474              |
| WHO universal trial number (UTN)   | U1111-1124-1167          |
| Other trial identifiers            | STUDY NAME: ODYSSEY MONO |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi aventis recherche & développement   |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380                               |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 03 October 2013 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 09 July 2013    |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab (SAR236553/REGN727) every 2 weeks (Q2W) as monotherapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in subjects with hypercholesterolemia at moderate cardiovascular (CV) risk.

Protection of trial subjects:

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

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

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Background therapy:

Concomitant medications were to be kept to a minimum during the study. However, if they were considered necessary for the subject's welfare, and were unlikely to interfere with the investigational medicinal product (IMPs), they could be given at a stable dose (when possible), at the discretion of the Investigator.

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Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 02 July 2012 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 15       |
| Country: Number of subjects enrolled | Finland: 11       |
| Country: Number of subjects enrolled | Netherlands: 28   |
| Country: Number of subjects enrolled | United States: 49 |
| Worldwide total number of subjects   | 103               |
| EEA total number of subjects         | 54                |

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)                      | 84 |
| From 65 to 84 years                       | 19 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 8 centers in 4 countries. A total of 204 subjects were screened between July 2012 and November 2012, 101 of whom were screen failures. Screen failures were mainly due to exclusion criteria met.

### Pre-assignment

Screening details:

Randomization was stratified according to the diabetes mellitus status. Assignment to treatment arms was done centrally using an Interactive Voice/Web Response System in a 1:1 ( alirocumab:ezetimibe) ratio after confirmation of selection criteria. 103 subjects were randomized.

### Period 1

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

Blinding implementation details:

Alirocumab and placebo for alirocumab were provided in identically matched autoinjectors and packaged identically. Ezetimibe double-blind treatment kit boxes, either ezetimibe 10 mg or placebo for ezetimibe, had the same appearance and feel and were labeled with a double-blind label.

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Ezetimibe 10 mg |

Arm description:

Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.

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

Dosage and administration details:

One over-encapsulated tablet once daily.

|  |                          |
|--|--------------------------|
| Investigational medicinal product name | Placebo (for alirocumab) |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh, or outer area of the upper arm by self-injection.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Alirocumab 75/Up to 150 mg Q2W |
|------------------|--------------------------------|

Arm description:

Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels  $\geq 70$  mg/dL (1.81 mmol/L) at Week 8.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Alirocumab             |
| Investigational medicinal product code | SAR236553, REGN727     |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

1 mL subcutaneous injection in the abdomen, thigh, or outer area of the upper arm by self--injection.

|  |                         |
|--|-------------------------|
| Investigational medicinal product name | Placebo (for Ezetimibe) |
| Investigational medicinal product code |                         |
| Other name                             |                         |
| Pharmaceutical forms                   | Capsule                 |
| Routes of administration               | Oral use                |

Dosage and administration details:

One capsule once daily.

| <b>Number of subjects in period 1</b> | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |
|---------------------------------------|-----------------|--------------------------------|
| Started                               | 51              | 52                             |
| Completed                             | 44              | 44                             |
| Not completed                         | 7               | 8                              |
| Consent withdrawn by subject          | -               | 1                              |
| 'Other than specified '               | 2               | 1                              |
| Adverse Event                         | 4               | 5                              |
| Poor compliance to protocol           | 1               | -                              |
| Patient moved                         | -               | 1                              |

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe 10 mg |
|-----------------------|-----------------|

Reporting group description:

Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Alirocumab 75/Up to 150 mg Q2W |
|-----------------------|--------------------------------|

Reporting group description:

Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels  $\geq 70$  mg/dL (1.81 mmol/L) at Week 8.

| Reporting group values | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W | Total |
|------------------------|-----------------|--------------------------------|-------|
| Number of subjects     | 51              | 52                             | 103   |
| Age categorical        |                 |                                |       |
| Units: Subjects        |                 |                                |       |

|   |            |            |    |
|---|------------|------------|----|
| Age continuous                            |            |            |    |
| Units: years                              |            |            |    |
| arithmetic mean                           | 59.6       | 60.8       |    |
| standard deviation                        | $\pm 5.3$  | $\pm 4.6$  | -  |
| Gender categorical                        |            |            |    |
| Units: Subjects                           |            |            |    |
| Female                                    | 24         | 24         | 48 |
| Male                                      | 27         | 28         | 55 |
| Calculated LDL-C in mg/dL                 |            |            |    |
| Calculated LDL-C from Friedewald formula. |            |            |    |
| Units: mg/dL                              |            |            |    |
| arithmetic mean                           | 138.3      | 141.1      |    |
| standard deviation                        | $\pm 24.5$ | $\pm 27.1$ | -  |
| Calculated LDL-C in mmol/L                |            |            |    |
| Units: mmol/L                             |            |            |    |
| arithmetic mean                           | 3.58       | 3.65       |    |
| standard deviation                        | $\pm 0.6$  | $\pm 0.7$  | -  |

## End points

### End points reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | Ezetimibe 10 mg                |
| Reporting group description:<br>Oral ezetimibe 10 mg daily and subcutaneous placebo (for alirocumab) every 2 weeks (Q2W) for 24 weeks.   |                                |
| Reporting group title  | Alirocumab 75/Up to 150 mg Q2W |
| Reporting group description:<br>Subcutaneous alirocumab 75 mg Q2W and oral placebo for ezetimibe for 24 weeks. Alirocumab dose up-titrated to 150 mg from Week 12 when LDL-C levels $\geq 70$ mg/dL (1.81 mmol/L) at Week 8. |                                |
| Subject analysis set title   | Ezetimibe 10 mg                |
| Subject analysis set type  | Safety analysis                |
| Subject analysis set description:<br>Subjects exposed to Ezetimibe 10 mg (mean exposure of 22 weeks).  |                                |
| Subject analysis set title   | Alirocumab 75/Up to 150 mg Q2W |
| Subject analysis set type  | Safety analysis                |
| Subject analysis set description:<br>Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W (mean exposure of 22 weeks).  |                                |

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

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-Treat (ITT) Analysis |
| End point description:<br>Calculated LDL-C values were obtained using the Friedwald formula. Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment. |  |
| End point type  | Primary  |
| End point timeframe:<br>From Baseline to Week 24  |  |

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 51                 | 52                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -15.6 ( $\pm$ 3.1) | -47.2 ( $\pm$ 3)               |  |  |

### Statistical analyses

|  |                         |
|--|-------------------------|
| Statistical analysis title   | Alirocumab vs Ezetimibe |
| Statistical analysis description:<br>Alirocumab group was compared to ezetimibe group using an appropriate contrast statement. |                         |

|   |  |
|---|--|
| Comparison groups                       | Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 103  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.0001 <sup>[1]</sup>                          |
| Method                                  | Mixed models analysis                            |
| Parameter estimate                      | LS mean difference                               |
| Point estimate                          | -31.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -40.2  |
| upper limit                             | -23  |

Notes:

[1] - Threshold for significance was  $\leq 0.05$ .

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

|  |  |
|--|--|
| End point title  | Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis |
| End point description:   |  |
| Adjusted LS means and standard errors at Week 12 from MMRM including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment (ITT analysis). ITT population. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From Baseline to Week 24   |  |

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 51                 | 52                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -19.6 ( $\pm$ 2.6) | -48.1 ( $\pm$ 2.6)             |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Alirocumab vs Ezetimibe                          |
| Statistical analysis description:  |  |
| A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 0.05 level. |  |
| Comparison groups  | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 103                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[2]</sup> |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | LS mean difference      |
| Point estimate                          | -28.5                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -35.7                   |
| upper limit                             | -21.2                   |

Notes:

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

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

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

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment.

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

End point timeframe:

From Baseline to Week 24

| End point values                    | Ezetimibe 10 mg  | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                |  |  |
| Number of subjects analysed         | 46               | 48                             |  |  |
| Units: percent change               |                  |                                |  |  |
| least squares mean (standard error) | -11 ( $\pm$ 2.4) | -36.7 ( $\pm$ 2.3)             |  |  |

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

|                   |  |
|-------------------|--|
| Comparison groups | Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 94                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[3]</sup> |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | LS mean difference      |
| Point estimate                          | -25.8                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -32.3                   |
| upper limit                             | -19.2                   |

Notes:

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

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

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

End point description:

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

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

End point timeframe:

From Baseline to Week 24

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 51                 | 52                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -15.1 ( $\pm$ 2.9) | -40.6 ( $\pm$ 2.8)             |  |  |

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

|                   |  |
|-------------------|--|
| Comparison groups | Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 103                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[4]</sup> |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | LS mean difference      |
| Point estimate                          | -25.5                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -33.5                   |
| upper limit                             | -17.4                   |

Notes:

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

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

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis |
|-----------------|---|

End point description:

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

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

End point timeframe:

From Baseline to Week 24

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 51                 | 52                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -10.9 ( $\pm$ 2.2) | -29.6 ( $\pm$ 2.1)             |  |  |

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

|                   |  |
|-------------------|--|
| Comparison groups | Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg |
|-------------------|--|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 103                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[5]</sup> |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | LS mean difference      |
| Point estimate                          | -18.7                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -24.7                   |
| upper limit                             | -12.7                   |

Notes:

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

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo B ITT population.

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

End point timeframe:

From Baseline to Week 24

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 46                 | 48                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -11.7 ( $\pm$ 2.1) | -37.3 ( $\pm$ 2.1)             |  |  |

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

|   |  |
|---|--|
| Comparison groups                       | Alirocumab 75/Up to 150 mg Q2W v Ezetimibe 10 mg |
| Number of subjects included in analysis | 94   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.0001 <sup>[6]</sup>                          |
| Method                                  | Mixed models analysis                            |
| Parameter estimate                      | LS mean difference                               |
| Point estimate                          | -25.7  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -31.5   |
| upper limit         | -19.8   |

Notes:

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

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

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in non-HDL-C at Week 12 - ITT Analysis |
| End point description:  |   |
| Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. non-HDL-C ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From Baseline to Week 24  |   |

| End point values                    | Ezetimibe 10 mg    | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|--------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group                |  |  |
| Number of subjects analysed         | 51                 | 52                             |  |  |
| Units: percent change               |                    |                                |  |  |
| least squares mean (standard error) | -16.7 ( $\pm$ 2.4) | -42.5 ( $\pm$ 2.3)             |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Alirocumab vs Ezetimibe                          |
| Statistical analysis description:  |  |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). |  |
| Comparison groups  | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |
| Number of subjects included in analysis  | 103  |
| Analysis specification   | Pre-specified                                    |
| Analysis type  | superiority                                      |
| P-value  | < 0.0001 <sup>[7]</sup>                          |
| Method   | Mixed models analysis                            |
| Parameter estimate   | LS mean difference                               |
| Point estimate   | -25.8  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -32.4  |
| upper limit  | -19.2  |

Notes:

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

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

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

End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Total-C ITT population.

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

End point timeframe:

From Baseline to Week 24

| End point values                    | Ezetimibe 10 mg   | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|-------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group                |  |  |
| Number of subjects analysed         | 51                | 52                             |  |  |
| Units: percent change               |                   |                                |  |  |
| least squares mean (standard error) | -12 ( $\pm 1.7$ ) | -30.3 ( $\pm 1.7$ )            |  |  |

### Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

|                   |  |
|-------------------|--|
| Comparison groups | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |
|-------------------|--|

|   |     |
|---|-----|
| Number of subjects included in analysis | 103 |
|---|-----|

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

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

|         |                           |
|---------|---------------------------|
| P-value | $< 0.0001$ <sup>[8]</sup> |
|---------|---------------------------|

|        |                       |
|--------|-----------------------|
| Method | Mixed models analysis |
|--------|-----------------------|

|                    |                    |
|--------------------|--------------------|
| Parameter estimate | LS mean difference |
|--------------------|--------------------|

|                |       |
|----------------|-------|
| Point estimate | -18.3 |
|----------------|-------|

Confidence interval

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

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

|             |       |
|-------------|-------|
| lower limit | -23.1 |
|-------------|-------|

|             |       |
|-------------|-------|
| upper limit | -13.5 |
|-------------|-------|

Notes:

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

### Secondary: Percentage of Subjects Achieving Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Achieving Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to Week 24

| End point values              | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------|-----------------|--------------------------------|--|--|
| Subject group type            | Reporting group | Reporting group                |  |  |
| Number of subjects analysed   | 51              | 52                             |  |  |
| Units: percentage of subjects |                 |                                |  |  |
| number (not applicable)       | 32.2            | 88.1                           |  |  |

## Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

|   |  |
|---|--|
| Comparison groups                       | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |
| Number of subjects included in analysis | 103  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.0001 <sup>[9]</sup>                          |
| Method                                  | Regression, Logistic                             |
| Parameter estimate                      | Odds ratio (OR)                                  |
| Point estimate                          | 34.8   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 8.7  |
| upper limit                             | 139  |

Notes:

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

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

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

End point description:

Adjusted percentages from multiple imputation approach including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. ITT population.

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

End point timeframe:

Up to Week 24

| <b>End point values</b>       | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------|-----------------|--------------------------------|--|--|
| Subject group type            | Reporting group | Reporting group                |  |  |
| Number of subjects analysed   | 51              | 52                             |  |  |
| Units: percentage of subjects |                 |                                |  |  |
| number (not applicable)       | 2.4             | 59.4                           |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>  | Alirocumab vs Ezetimibe                          |
|--|--|
| Statistical analysis description:  |  |
| Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). |  |
| Comparison groups  | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |
| Number of subjects included in analysis  | 103  |
| Analysis specification   | Pre-specified                                    |
| Analysis type  | superiority                                      |
| P-value  | = 0.0001 <sup>[10]</sup>                         |
| Method   | Regression, Logistic                             |
| Parameter estimate   | Odds ratio (OR)                                  |
| Point estimate   | 69.8   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 8.8  |
| upper limit  | 556  |

Notes:

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

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

| <b>End point title</b>   | Percent Change From Baseline in Lipoprotein (a) at Week 24 - ITT Analysis |
|--|---|
| End point description:   |   |
| Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. |   |
| Subjects analyzed: subjects of the ITT population.   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Baseline to Week 24   |   |



| End point values                 | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|----------------------------------|-----------------|--------------------------------|--|--|
| Subject group type               | Reporting group | Reporting group                |  |  |
| Number of subjects analysed      | 51              | 52                             |  |  |
| Units: percent change            |                 |                                |  |  |
| arithmetic mean (standard error) | -12.3 (± 3.8)   | -16.7 (± 3.7)                  |  |  |

## Statistical analyses

| Statistical analysis title | Alirocumab vs Ezetimibe |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

|   |  |
|---|--|
| Comparison groups                       | Ezetimibe 10 mg v Alirocumab 75/Up to 150 mg Q2W |
| Number of subjects included in analysis | 103  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.4013 <sup>[11]</sup>                         |
| Method                                  | Regression, Robust                               |
| Parameter estimate                      | Adjusted Mean Difference                         |
| Point estimate                          | -4.4   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -14.8  |
| upper limit                             | 5.9  |

Notes:

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

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

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

End point description:

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

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From Baseline to Week 24 |           |

| End point values                    | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|-----------------|--------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                |  |  |
| Number of subjects analysed         | 51              | 52                             |  |  |
| Units: percent change               |                 |                                |  |  |
| least squares mean (standard error) | 1.6 (± 1.9)     | 6 (± 1.9)                      |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. HDL-C ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 24  |   |

| End point values                    | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|-----------------|--------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                |  |  |
| Number of subjects analysed         | 51              | 52                             |  |  |
| Units: percent change               |                 |                                |  |  |
| least squares mean (standard error) | 1.6 (± 2)       | 9 (± 2)                        |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis |
| End point description:<br>Adjusted means and standard errors at Week 12 from from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population. |   |
| End point type   | Secondary   |
| End point timeframe:<br>From Baseline Week 24  |   |

| End point values                 | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|----------------------------------|-----------------|--------------------------------|--|--|
| Subject group type               | Reporting group | Reporting group                |  |  |
| Number of subjects analysed      | 51              | 52                             |  |  |
| Units: percent change            |                 |                                |  |  |
| arithmetic mean (standard error) | -14.2 (± 3.7)   | -17.2 (± 3.7)                  |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis |
| End point description:<br>Adjusted means and standard errors at Week 24 from multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline Week 24   |   |

| End point values                 | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |  |
|----------------------------------|-----------------|--------------------------------|--|--|
| Subject group type               | Reporting group | Reporting group                |  |  |
| Number of subjects analysed      | 51              | 52                             |  |  |
| Units: percent change            |                 |                                |  |  |
| arithmetic mean (standard error) | -10.8 (± 4.3)   | -11.9 (± 4.2)                  |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis |
| End point description:<br>Adjusted means and standard errors at Week 12 from multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Fasting |   |

triglycerides ITT population.

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From Baseline to Week 24 |           |

| End point values                 | Ezetimibe 10 mg   | Alirocumab 75/Up to 150 mg Q2W |  |  |
|----------------------------------|-------------------|--------------------------------|--|--|
| Subject group type               | Reporting group   | Reporting group                |  |  |
| Number of subjects analysed      | 51                | 52                             |  |  |
| Units: percent change            |                   |                                |  |  |
| arithmetic mean (standard error) | -2.3 ( $\pm$ 3.5) | -12.2 ( $\pm$ 3.4)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Apoprotein A-1 (Apo A-1) at Week 24 - ITT Analysis

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in Apoprotein A-1 (Apo A-1) at Week 24 - ITT Analysis |
|-----------------|--|

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo A-1 value on- or off-treatment.

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From Baseline to Week 24 |           |

| End point values                    | Ezetimibe 10 mg   | Alirocumab 75/Up to 150 mg Q2W |  |  |
|-------------------------------------|-------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group                |  |  |
| Number of subjects analysed         | 46                | 48                             |  |  |
| Units: percent change               |                   |                                |  |  |
| least squares mean (standard error) | -0.6 ( $\pm$ 1.6) | 4.7 ( $\pm$ 1.6)               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis

|   |   |
|---|---|
| End point title   | Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis |
| End point description:<br>Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo A-1 ITT population. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Baseline to Week 24  |   |

| End point values                 | Ezetimibe 10 mg   | Alirocumab 75/Up to 150 mg Q2W |  |  |
|----------------------------------|-------------------|--------------------------------|--|--|
| Subject group type               | Reporting group   | Reporting group                |  |  |
| Number of subjects analysed      | 46                | 48                             |  |  |
| Units: percent change            |                   |                                |  |  |
| arithmetic mean (standard error) | -2.2 ( $\pm$ 1.4) | 2.3 ( $\pm$ 1.4)               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 32) regardless of seriousness or relationship to investigational medicinal product (IMP).

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (from the first dose of double-blind IMP administration (capsule or injection, whichever came first) up the day of the last double-blind IMP injection + 70 days).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Ezetimibe 10 mg |
|-----------------------|-----------------|

Reporting group description:

Subjects exposed to Ezetimibe 10 mg (mean exposure of 22 weeks).

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Alirocumab 75/Up to 150 mg Q2W |
|-----------------------|--------------------------------|

Reporting group description:

Subjects exposed to Alirocumab 75 mg/Up to 150 mg Q2W (mean exposure of 22 weeks).

| Serious adverse events                            | Ezetimibe 10 mg | Alirocumab 75/Up to 150 mg Q2W |  |
|---|-----------------|--------------------------------|--|
| Total subjects affected by serious adverse events |                 |                                |  |
| subjects affected / exposed                       | 1 / 51 (1.96%)  | 1 / 52 (1.92%)                 |  |
| number of deaths (all causes)                     | 0               | 0                              |  |
| number of deaths resulting from adverse events    |                 |                                |  |
| Respiratory, thoracic and mediastinal disorders   |                 |                                |  |
| Pulmonary Embolism                                |                 |                                |  |
| subjects affected / exposed                       | 0 / 51 (0.00%)  | 1 / 52 (1.92%)                 |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1                          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                          |  |
| Musculoskeletal and connective tissue disorders   |                 |                                |  |
| Bone Erosion                                      |                 |                                |  |
| subjects affected / exposed                       | 1 / 51 (1.96%)  | 0 / 52 (0.00%)                 |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0                          |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                          |  |

| <b>Non-serious adverse events</b>                     | Ezetimibe 10 mg  | Alirocumab 75/Up to 150 mg Q2W |  |
|---|------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events |                  |                                |  |
| subjects affected / exposed                           | 27 / 51 (52.94%) | 25 / 52 (48.08%)               |  |
| Nervous system disorders                              |                  |                                |  |
| Dizziness   |                  |                                |  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   | 1 / 52 (1.92%)                 |  |
| occurrences (all)                                     | 3                | 1                              |  |
| Headache  |                  |                                |  |
| subjects affected / exposed                           | 2 / 51 (3.92%)   | 3 / 52 (5.77%)                 |  |
| occurrences (all)                                     | 2                | 5                              |  |
| Gastrointestinal disorders                            |                  |                                |  |
| Diarrhoea   |                  |                                |  |
| subjects affected / exposed                           | 2 / 51 (3.92%)   | 6 / 52 (11.54%)                |  |
| occurrences (all)                                     | 2                | 6                              |  |
| Nausea  |                  |                                |  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   | 3 / 52 (5.77%)                 |  |
| occurrences (all)                                     | 3                | 5                              |  |
| Musculoskeletal and connective tissue disorders       |                  |                                |  |
| Arthralgia  |                  |                                |  |
| subjects affected / exposed                           | 2 / 51 (3.92%)   | 3 / 52 (5.77%)                 |  |
| occurrences (all)                                     | 2                | 3                              |  |
| Back Pain   |                  |                                |  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   | 1 / 52 (1.92%)                 |  |
| occurrences (all)                                     | 3                | 1                              |  |
| Infections and infestations                           |                  |                                |  |
| Influenza   |                  |                                |  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   | 6 / 52 (11.54%)                |  |
| occurrences (all)                                     | 3                | 6                              |  |
| Nasopharyngitis                                       |                  |                                |  |
| subjects affected / exposed                           | 8 / 51 (15.69%)  | 12 / 52 (23.08%)               |  |
| occurrences (all)                                     | 9                | 16                             |  |
| Upper Respiratory Tract Infection                     |                  |                                |  |
| subjects affected / exposed                           | 5 / 51 (9.80%)   | 2 / 52 (3.85%)                 |  |
| occurrences (all)                                     | 6                | 2                              |  |
| Urinary Tract Infection                               |                  |                                |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 3 / 51 (5.88%) | 0 / 52 (0.00%) |  |
| occurrences (all)           | 3              | 0              |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 11 February 2013 | <ol style="list-style-type: none"><li>1. Change in reporting of adverse events<ul style="list-style-type: none"><li>- safety reporting timelines was changed from "within 1 working day" to "within 24 hours" for serious adverse events and adverse events of special interest (AESI) with immediate notification.</li><li>- Addition of pregnancy of male subject's partner as an AESI with immediate notification.</li></ul></li><li>2. Clarification for some safety laboratory parameters<ul style="list-style-type: none"><li>- Red blood cell distribution width and reticulocyte count added as hematology laboratory parameters.</li><li>- Reticulocyte count no longer assessed reflexively but rather systematically on all study samples.</li></ul></li><li>3. Precision added in the definition of the investigational medicinal product – ezetimibe capsule.</li><li>4. Highlighted the need for an effective method of contraception in women of childbearing potential throughout the study treatment.</li></ol> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Due to administrative error in the automated process (which was detected after database lock), planned dose up-titration criteria for LDL-C levels was changed from  $\geq 100$  mg/dL to  $\geq 70$  mg/dL.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25606700>