



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients With Homozygous Familial Hypercholesterolemia

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-000351-95   |
| Trial protocol           | FR AT GR IT      |
| Global end of trial date | 13 February 2020 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 26 February 2021 |
| First version publication date | 26 February 2021 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | R727-CL-1628 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03156621 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Regeneron Pharmaceuticals, Inc.  |
| Sponsor organisation address | 777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591                              |
| Public contact               | Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com |
| Scientific contact           | Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.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                       | 13 February 2020 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) with alirocumab subcutaneous (SC) every 2 weeks (Q2W) in comparison to placebo after 12 weeks of treatment.

The secondary objectives of the study were:

To evaluate the effect of alirocumab Q2W on other lipid parameters (ie, apolipoprotein [Apo] A-1 and B, non-high-density lipoprotein cholesterol [non-HDL-C], total-cholesterol [TC], proportion of subjects with 15%, 30%, and 50% LDL-C reductions, Lp(a), HDL-C, triglycerides [TG]) in subjects with HoFH  
To evaluate the safety and tolerability of alirocumab SC Q2W in subjects with HoFH  
To assess the pharmacokinetics of alirocumab SC Q2W in subjects with HoFH  
To assess the potential development of anti-drug (alirocumab) antibodies (ADA)

Protection of trial subjects:

This clinical study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 03 October 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Austria: 3       |
| Country: Number of subjects enrolled | Canada: 5        |
| Country: Number of subjects enrolled | Czechia: 4       |
| Country: Number of subjects enrolled | France: 3        |
| Country: Number of subjects enrolled | Germany: 1       |
| Country: Number of subjects enrolled | Greece: 6        |
| Country: Number of subjects enrolled | Italy: 8         |
| Country: Number of subjects enrolled | Japan: 8         |
| Country: Number of subjects enrolled | South Africa: 6  |
| Country: Number of subjects enrolled | Taiwan: 4        |
| Country: Number of subjects enrolled | Turkey: 5        |
| Country: Number of subjects enrolled | Ukraine: 10      |
| Country: Number of subjects enrolled | United States: 6 |

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 69 |
| EEA total number of subjects       | 25 |

Notes:

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**Subjects enrolled per age group**

|   |    |
|---|----|
| 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)                      | 61 |
| From 65 to 84 years                       | 8  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited from 27 centers in 13 countries around Europe, Asia, South Africa, and North America. A total of 85 subjects were screened. Of those, 16 were considered screen failures (mainly due to violations of inclusion/exclusion criteria).

### Pre-assignment

Screening details:

Sixty-nine of the 85 subjects were eligible and randomized in a 2:1 ratio to receive either alirocumab 150 mg SC Q2W or matching placebo. Randomization was stratified by apheresis treatment status (Yes/No).

### Period 1

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

### Arms

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

Arm description:

Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period.

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

Dosage and administration details:

Matching placebo SC Q2W

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

Arm description:

Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.

|  |                                 |
|--|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | Alirocumab                      |
| Investigational medicinal product code |                                 |
| Other name                             | PRALUENT® REGN727 SAR236553     |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Subcutaneous use                |

Dosage and administration details:

Alirocumab SC Q2W

| Number of subjects in period 1 | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |
|--------------------------------|-----------------|----------------------------------|
| Started                        | 24              | 45                               |
| Completed                      | 24              | 45                               |

## Period 2

|                              |                                    |
|------------------------------|------------------------------------|
| Period 2 title               | Open-Label Treatment Period (OLTP) |
| Is this the baseline period? | No                                 |
| Allocation method            | Non-randomised - controlled        |
| Blinding used                | Not blinded                        |

## Arms

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

Arm description:

Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W

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

Dosage and administration details:

Matching placebo SC Q2W

\*\*Not administered in OLTP, only administered in DBTP

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

Arm description:

Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Alirocumab                        |
| Investigational medicinal product code |                                   |
| Other name                             | PRALUENT®<br>REGN727<br>SAR236553 |
| Pharmaceutical forms                   | Solution for injection/infusion   |
| Routes of administration               | Subcutaneous use                  |

Dosage and administration details:

150 mg SC Q2W

| <b>Number of subjects in period 2</b> | Placebo in DBTP | Alirocumab 150 mg<br>SC Q2W |
|---------------------------------------|-----------------|-----------------------------|
| Started                               | 24              | 45                          |
| Completed                             | 24              | 42                          |
| Not completed                         | 0               | 3                           |
| Consent withdrawn by subject          | -               | 1                           |
| Adverse event, non-fatal              | -               | 2                           |

## Baseline characteristics

### Reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | Placebo in DBTP                  |
| Reporting group description:   |                                  |
| Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. |                                  |
| Reporting group title  | Alirocumab 150 mg SC Q2W in DBTP |
| Reporting group description:   |                                  |
| Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.        |                                  |

| Reporting group values                             | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP | Total |
|--|-----------------|----------------------------------|-------|
| Number of subjects                                 | 24              | 45                               | 69    |
| Age categorical                                    |                 |                                  |       |
| Units: Subjects                                    |                 |                                  |       |
| In utero   | 0               | 0                                | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0               | 0                                | 0     |
| Newborns (0-27 days)                               | 0               | 0                                | 0     |
| Infants and toddlers (28 days-23 months)           | 0               | 0                                | 0     |
| Children (2-11 years)                              | 0               | 0                                | 0     |
| Adolescents (12-17 years)                          | 0               | 0                                | 0     |
| Adults (18-64 years)                               | 20              | 41                               | 61    |
| From 65-84 years                                   | 4               | 4                                | 8     |
| 85 years and over                                  | 0               | 0                                | 0     |
| Age Continuous                                     |                 |                                  |       |
| Units: Years                                       |                 |                                  |       |
| arithmetic mean                                    | 45.4            | 42.3                             |       |
| standard deviation                                 | ± 15.80         | ± 14.13                          | -     |
| Sex: Female, Male                                  |                 |                                  |       |
| Units: Participants                                |                 |                                  |       |
| Female   | 11              | 24                               | 35    |
| Male   | 13              | 21                               | 34    |
| Race/Ethnicity, Customized                         |                 |                                  |       |
| Units: Subjects                                    |                 |                                  |       |
| White  | 18              | 36                               | 54    |
| Black or African American                          | 0               | 2                                | 2     |
| Asian  | 5               | 7                                | 12    |
| American Indian or Alaska Native                   | 0               | 0                                | 0     |
| Native Hawaiian or Other Pacific Islander          | 0               | 0                                | 0     |
| Other  | 1               | 0                                | 1     |
| Ethnicity (NIH/OMB)                                |                 |                                  |       |
| Units: Subjects                                    |                 |                                  |       |
| Hispanic or Latino                                 | 0               | 2                                | 2     |
| Not Hispanic or Latino                             | 24              | 43                               | 67    |
| Unknown or Not Reported                            | 0               | 0                                | 0     |

|  |                   |                   |   |
|--|-------------------|-------------------|---|
| Low-density lipoprotein cholesterol (LDL-C)<br>Units: milligram/deciliter (mg/dL)<br>arithmetic mean<br>standard deviation | 259.6<br>± 175.75 | 295.0<br>± 154.59 | - |
| Non-high-density lipoprotein cholesterol (Non-HDL-C)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation              | 282.0<br>± 177.41 | 320.5<br>± 160.36 | - |
| Total-cholesterol (Total-C)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation                                       | 325.1<br>± 171.57 | 364.3<br>± 157.30 | - |
| High-density lipoprotein cholesterol (HDL-C)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation                      | 43.2<br>± 11.96   | 43.8<br>± 14.78   | - |
| Fasting triglycerides (TG)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation  | 111.7<br>± 77.97  | 128.0<br>± 74.34  | - |
| Lipoprotein(a) [Lp(a)]<br>Units: mg/dL<br>arithmetic mean<br>standard deviation  | 40.0<br>± 36.41   | 42.9<br>± 36.34   | - |
| Apolipoprotein-B (Apo-B)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation  | 175.0<br>± 95.12  | 193.3<br>± 87.59  | - |
| Apolipoprotein-A1 (Apo-A1)<br>Units: mg/dL<br>arithmetic mean<br>standard deviation  | 124.8<br>± 24.59  | 125.6<br>± 28.57  | - |
| Apo-B/Apo-A1<br>Units: ratio<br>arithmetic mean<br>standard deviation  | 1.590<br>± 1.4746 | 1.635<br>± 0.8693 | - |



## End points

### End points reporting groups

|  |                                  |
|--|----------------------------------|
| Reporting group title  | Placebo in DBTP                  |
| Reporting group description:<br>Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period.   |                                  |
| Reporting group title  | Alirocumab 150 mg SC Q2W in DBTP |
| Reporting group description:<br>Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period.  |                                  |
| Reporting group title  | Placebo in DBTP                  |
| Reporting group description:<br>Subjects received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W |                                  |
| Reporting group title  | Alirocumab 150 mg SC Q2W         |
| Reporting group description:<br>Subjects in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all subjects received open-label alirocumab SC Q2W        |                                  |
| Subject analysis set title   | Alirocumab 150 mg SC Q2W in OLTP |
| Subject analysis set type  | Safety analysis                  |
| Subject analysis set description:<br>Subjects who received at least 1 dose or part of a dose of open-label investigational study drug alirocumab in OLTP   |                                  |

### Primary: Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 (Intent-to-Treat [ITT] estimand)

|  |   |
|--|---|
| End point title  | Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to week 12 (Intent-to-Treat [ITT] estimand) |
| End point description:<br>The percent change in LDL-C from baseline to week 12 is defined as: $100 \times (\text{LDL-C value at week 12} - \text{LDL-C value at baseline}) / \text{LDL-C value at baseline}$ . |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 8.6 (± 6.3)     | -26.9 (± 4.6)                    |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[1]</sup>                            |
| Method                                  | MMRM   |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -35.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -51.2  |
| upper limit                             | -19.9  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 7.8  |

Notes:

[1] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis

### Secondary: Percent change in apolipoprotein (Apo) B from baseline to week 12 (ITT estimand)

|                        |  |
|------------------------|--|
| End point title        | Percent change in apolipoprotein (Apo) B from baseline to week 12 (ITT estimand)   |
| End point description: | ITT estimand; The percent change in Apo B from baseline to week 12 is defined as: 100x (Apo B value at week 12 - Apo B value at baseline) / Apo B value at baseline. |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline to Week 12    |  |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 7.2 (± 5.0)     | -22.5 (± 3.7)                    |  |  |

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                 | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |

|   |                                    |
|---|------------------------------------|
| Number of subjects included in analysis | 69                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | < 0.0001 <sup>[2]</sup>            |
| Method                                  | MMRM                               |
| Parameter estimate                      | Least squares (LS) mean difference |
| Point estimate                          | -29.8                              |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -42.3                              |
| upper limit                             | -17.3                              |
| Variability estimate                    | Standard error of the mean         |
| Dispersion value                        | 6.3                                |

Notes:

[2] - p-value taken from MMRM (mixed-effect model with repeated measures) analysis

### Secondary: Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to week 12

|                        |  |
|------------------------|--|
| End point title        | Percent change in non-high-density lipoprotein cholesterol (non-HDL-C) from baseline to week 12  |
| End point description: | ITT estimand; The percent change in non-HDL-C from baseline to week 12 is defined as: 100x (non-HDL-C value at week 12 - non-HDL-C value at baseline) / non-HDL-C value at baseline. |
| End point type         | Secondary  |
| End point timeframe:   | Baseline to Week 12  |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 8.0 (± 5.9)     | -24.8 (± 4.3)                    |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[3]</sup>                            |
| Method                                  | MMRM   |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -32.9  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -47.6                      |
| upper limit          | -18.2                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 7.4                        |

Notes:

[3] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis

## Secondary: Percent change in total cholesterol (TC) from baseline to week 12

|  |   |
|--|---|
| End point title  | Percent change in total cholesterol (TC) from baseline to week 12 |
| End point description:   |   |
| ITT estimand; The percent change in TC from baseline to week 12 is defined as: $100 \times (\text{TC value at week 12} - \text{TC value at baseline}) / \text{TC value at baseline}$ . |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP  | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                  |  |  |
| Number of subjects analysed         | 24               | 45                               |  |  |
| Units: Percentage                   |                  |                                  |  |  |
| least squares mean (standard error) | 6.6 ( $\pm$ 5.0) | -19.8 ( $\pm$ 3.7)               |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001 <sup>[4]</sup>                            |
| Method                                  | MMRM   |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -26.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -38.9  |
| upper limit                             | -14  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 6.2  |

Notes:

[4] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis.

### Secondary: Proportion of subjects with $\geq 15\%$ reduction in LDL-C at week 12

|                        |   |
|------------------------|---|
| End point title        | Proportion of subjects with $\geq 15\%$ reduction in LDL-C at week 12 |
| End point description: |   |
| ITT estimand           |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| At Week 12             |   |

| End point values            | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-----------------------------|-----------------|----------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed | 24              | 45                               |  |  |
| Units: Percentage           |                 |                                  |  |  |
| number (not applicable)     | 12.5            | 61.9                             |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.0004   |
| Method                                  | Regression, Logistic                               |
| Parameter estimate                      | Odds ratio (OR)                                    |
| Point estimate                          | 12.2   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 3.1  |
| upper limit                             | 48.8   |

### Secondary: Proportion of subjects with $\geq 30\%$ reduction in LDL-C at week 12

|                        |   |
|------------------------|---|
| End point title        | Proportion of subjects with $\geq 30\%$ reduction in LDL-C at week 12 |
| End point description: |   |
| ITT estimand           |   |
| End point type         | Secondary   |

End point timeframe:

At Week 12

| End point values            | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-----------------------------|-----------------|----------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed | 24              | 45                               |  |  |
| Units: Percentage           |                 |                                  |  |  |
| number (not applicable)     | 4.2             | 57.1                             |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.001  |
| Method                                  | Regression, Logistic                               |
| Parameter estimate                      | Log odds ratio                                     |
| Point estimate                          | 36.5   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 4.3  |
| upper limit                             | 308.9  |

### Secondary: Percent change in lipoprotein(a) [Lp(a)] from baseline to week 12

|  |   |
|--|---|
| End point title  | Percent change in lipoprotein(a) [Lp(a)] from baseline to week 12 |
| End point description:   |   |
| ITT estimand; The percent change in Lp(a) from baseline to week 12 is defined as: $100 \times (\text{Lp(a) value at week 12} - \text{Lp(a) value at baseline}) / \text{Lp(a) value at baseline}$ . |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 8.8 (± 5.4)     | -19.6 (± 4.0)                    |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | < 0.0001   |
| Method                                  | Regression model                                   |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | -28.4  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -41.5  |
| upper limit                             | -15.2  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 6.7  |

### Secondary: Proportion of subjects with ≥50% reduction in LDL-C at week 12

|                        |  |
|------------------------|--|
| End point title        | Proportion of subjects with ≥50% reduction in LDL-C at week 12 |
| End point description: |  |
| ITT estimand           |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| At Week 12             |  |

| End point values            | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-----------------------------|-----------------|----------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed | 24              | 45                               |  |  |
| Units: Percentage           |                 |                                  |  |  |
| number (not applicable)     | 0               | 26.7                             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.0017   |
| Method                                  | Exact Conditional Logistic Regression              |
| Parameter estimate                      | Odds ratio (OR)                                    |
| Point estimate                          | 17.7   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 3.3  |
| upper limit                             | 99999  |

## Secondary: Percent change in HDL-C from baseline to week 12 - ITT analysis

|  |   |
|--|---|
| End point title  | Percent change in HDL-C from baseline to week 12 - ITT analysis |
| End point description:<br>ITT estimand; The percent change in HDL-C from baseline to week 12 is defined as: $100 \times (\text{HDL-C value at week 12} - \text{HDL-C value at baseline}) / \text{HDL-C value at baseline}$ . |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP  | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                  |  |  |
| Number of subjects analysed         | 24               | 45                               |  |  |
| Units: Percentage                   |                  |                                  |  |  |
| least squares mean (standard error) | 2.7 ( $\pm$ 3.1) | 6.3 ( $\pm$ 2.3)                 |  |  |

## Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | = 0.3541 <sup>[5]</sup>                            |
| Method                                  | MMRM   |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | 3.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -4.1   |
| upper limit                             | 11.3   |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 3.8  |

Notes:

[5] - P-value taken from MMRM (mixed-effect model with repeated measures) analysis.

### Secondary: Percent change in fasting triglycerides (TG) from baseline to week 12

|                 |   |
|-----------------|---|
| End point title | Percent change in fasting triglycerides (TG) from baseline to week 12 |
|-----------------|---|

End point description:

ITT estimand; The percent change in TG from baseline to week 12 is defined as:  $100 \times (\text{TG value at week 12} - \text{TG value at baseline}) / \text{TG value at baseline}$ .

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

End point timeframe:

Baseline to Week 12

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 3.9 (± 5.7)     | -7.4 (± 4.2)                     |  |  |

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Alirocumab 150 SC Q2W vs. Placebo SC Q2W           |
| Comparison groups                 | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 69                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -11.3                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -25.2                          |
| upper limit                             | 2.6                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 7.1                            |

### Secondary: Percent change in Apo A-1 from baseline to week 12 -- ITT analysis

|  |  |
|--|--|
| End point title  | Percent change in Apo A-1 from baseline to week 12 -- ITT analysis |
| End point description:   |  |
| ITT estimand; The percent change in Apo A-1 from baseline to week 12 is defined as: $100 \times (\text{Apo A-1 value at week 12} - \text{Apo A-1 value at baseline}) / \text{Apo A-1 value at baseline}$ . |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline to Week 12  |  |

| End point values                    | Placebo in DBTP  | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                  |  |  |
| Number of subjects analysed         | 24               | 45                               |  |  |
| Units: Percentage                   |                  |                                  |  |  |
| least squares mean (standard error) | 1.4 ( $\pm$ 2.9) | 5.0 ( $\pm$ 2.1)                 |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | 3.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -3.6   |
| upper limit                             | 10.7   |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.6                        |

### Secondary: Percent change in LDL-C from baseline to week 12 (on-treatment estimand)

|                 |  |
|-----------------|--|
| End point title | Percent change in LDL-C from baseline to week 12 (on-treatment estimand) |
|-----------------|--|

End point description:

Percent change for LDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

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

End point timeframe:

Baseline to Week 12

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 8.6 (± 6.3)     | -26.9 (± 4.6)                    |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -35.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -51.2  |
| upper limit                             | -19.9  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 7.8  |

### Secondary: Percent change in Apo B from baseline to week 12 (on-treatment estimand)

|   |  |
|---|--|
| End point title   | Percent change in Apo B from baseline to week 12 (on-treatment estimand) |
| End point description:<br>Percent change for Apo B from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline to Week 12   |  |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 7.2 (± 5.0)     | -22.5 (± 3.7)                    |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -29.8  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -43.3  |
| upper limit                             | -17.3  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 6.3  |

### Secondary: Percent change in non-HDL-C from baseline to week 12 (on-treatment estimand)

|   |  |
|---|--|
| End point title   | Percent change in non-HDL-C from baseline to week 12 (on-treatment estimand) |
| End point description:<br>Percent change for non-HDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |  |
| End point type  | Secondary  |

End point timeframe:

Baseline to Week 12

| End point values                    | Placebo in DBTP  | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                  |  |  |
| Number of subjects analysed         | 24               | 45                               |  |  |
| Units: Percentage                   |                  |                                  |  |  |
| least squares mean (standard error) | 8.0 ( $\pm$ 5.9) | -24.8 ( $\pm$ 4.3)               |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -32.9  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -47.6  |
| upper limit                             | -18.2  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 7.4  |

### Secondary: Percent change in TC from baseline to week 12 (on-treatment estimand)

|  |   |
|--|---|
| End point title  | Percent change in TC from baseline to week 12 (on-treatment estimand) |
| End point description:   |   |
| Percent change for TC from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 6.6 (± 5.0)     | -19.8 (± 3.7)                    |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SQ Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -26.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -28.9  |
| upper limit                             | -14  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 6.2  |

### Secondary: Percent change in Lp(a) from baseline to week 12 (on-treatment estimand)

|                        |   |
|------------------------|---|
| End point title        | Percent change in Lp(a) from baseline to week 12 (on-treatment estimand)  |
| End point description: | Percent change for LP(a) from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12    |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 8.8 (± 5.4)     | -19.6 (± 4.0)                    |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | -28.4  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -41.5  |
| upper limit                             | -15.2  |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 6.7  |

## Secondary: Percent change in HDL-C from baseline to week 12 - (on-treatment estimand)

|   |  |
|---|--|
| End point title   | Percent change in HDL-C from baseline to week 12 - (on-treatment estimand) |
| End point description:  |  |
| Percent change for HDL-C from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline to Week 12   |  |

|                                     |                 |                                  |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| <b>End point values</b>             | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 2.7 (± 3.1)     | 6.3 (± 2.3)                      |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | 3.6  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -4.1   |
| upper limit                             | 11.3   |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 3.8  |

### Secondary: Percent change in fasting TG from baseline to week 12 (on-treatment estimand)

|  |   |
|--|---|
| End point title  | Percent change in fasting TG from baseline to week 12 (on-treatment estimand) |
| End point description:<br>Percent change for fasting TG from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline to Week 12  |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 3.9 (± 5.7)     | -7.4 (± 4.2)                     |  |  |

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                 | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 69                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -11.3                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -25.2                          |
| upper limit                             | 2.6                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 7.1                            |

### Secondary: Percent change in Apo A-1 from baseline to week 12 -- (on-treatment estimand)

|                        |   |
|------------------------|---|
| End point title        | Percent change in Apo A-1 from baseline to week 12 -- (on-treatment estimand)   |
| End point description: | Percent change for Apo A-1 from baseline to Week 12 during the efficacy treatment period, which is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier. |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 12    |   |

| End point values                    | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|-----------------|----------------------------------|--|--|
| Subject group type                  | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed         | 24              | 45                               |  |  |
| Units: Percentage                   |                 |                                  |  |  |
| least squares mean (standard error) | 1.4 (± 2.9)     | 5.0 (± 2.1)                      |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | 3.6  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -3.6                       |
| upper limit          | 10.7                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 3.6                        |

**Secondary: Proportion of subjects with  $\geq 15\%$  reduction,  $\geq 30\%$  reduction, and  $\geq 50\%$  reduction in LDL-C at week 12 (on-treatment estimand)**

|                        |   |
|------------------------|---|
| End point title        | Proportion of subjects with $\geq 15\%$ reduction, $\geq 30\%$ reduction, and $\geq 50\%$ reduction in LDL-C at week 12 (on-treatment estimand) |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| At Week 12             |   |

| End point values            | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-----------------------------|-----------------|----------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed | 24              | 45                               |  |  |
| Units: Percentage           |                 |                                  |  |  |
| number (not applicable)     |                 |                                  |  |  |
| $\geq 15\%$                 | 12.5            | 61.9                             |  |  |
| $\geq 30\%$                 | 4.2             | 57.1                             |  |  |
| $\geq 50\%$                 | 0               | 26.7                             |  |  |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Statistical analysis description:       |  |
| $\geq 15\%$ reduction                   |  |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Odds ratio (OR)                                    |
| Point estimate                          | 12.2   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 3.1     |
| upper limit         | 48.8    |

|  |  |
|--|--|
| <b>Statistical analysis title</b>                    | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Statistical analysis description:<br>≥ 30% reduction |  |
| Comparison groups                                    | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis              | 69   |
| Analysis specification                               | Pre-specified                                      |
| Analysis type  | superiority  |
| Parameter estimate                                   | Odds ratio (OR)                                    |
| Point estimate                                       | 36.5   |
| Confidence interval                                  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 4.3  |
| upper limit  | 308.9  |

|  |  |
|--|--|
| <b>Statistical analysis title</b>                    | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Statistical analysis description:<br>≥ 50% reduction |  |
| Comparison groups                                    | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis              | 69   |
| Analysis specification                               | Pre-specified                                      |
| Analysis type  | superiority  |
| Parameter estimate                                   | Odds ratio (OR)                                    |
| Point estimate                                       | 17.7   |
| Confidence interval                                  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 3.3  |
| upper limit  | 99999  |

|   |   |
|---|---|
| <b>Secondary: Absolute change in the ratio of Apo B/Apo A-1 from baseline to week 12 (ITT estimand)</b> |   |
| End point title   | Absolute change in the ratio of Apo B/Apo A-1 from baseline to week 12 (ITT estimand) |
| End point description:<br>ITT estimand  |   |
| End point type  | Secondary   |

End point timeframe:

Baseline to Week 12

| End point values                    | Placebo in DBTP  | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-------------------------------------|------------------|----------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                  |  |  |
| Number of subjects analysed         | 24               | 45                               |  |  |
| Units: Percentage                   |                  |                                  |  |  |
| least squares mean (standard error) | 0.0 ( $\pm$ 0.1) | -0.3 ( $\pm$ 0.1)                |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Alirocumab 150 mg SC Q2W vs. Placebo SC Q2W        |
| Comparison groups                       | Placebo in DBTP v Alirocumab 150 mg SC Q2W in DBTP |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Least squares (LS) mean difference                 |
| Point estimate                          | -0.3   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.6   |
| upper limit                             | -0.1   |
| Variability estimate                    | Standard error of the mean                         |
| Dispersion value                        | 0.1  |

### Secondary: Incidence of anti-drug antibodies (ADA) to REGN727 over time

|                 |   |
|-----------------|---|
| End point title | Incidence of anti-drug antibodies (ADA) to REGN727 over |
|-----------------|---|

End point description:

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

End point timeframe:

26 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to be summarized only for reported treatment group (s) in the table.

| End point values            | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP |  |  |
|-----------------------------|-----------------|----------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                  |  |  |
| Number of subjects analysed | 24              | 44                               |  |  |
| Units: Subjects             |                 |                                  |  |  |
| Treatment-Emergent          | 1               | 1                                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of Adverse Events (AEs)

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Incidence of Adverse Events (AEs) |
|-----------------|-----------------------------------|

End point description:

All AEs will be recorded from time of informed consent to end of study. Only treatment-emergent adverse events (TEAE) will be reported. Double-blind TEAE observation period is defined as time from first dose of double-blind study drug to last dose of double-blind study drug +70 days, or up to day before first dose of open-label study drug administration, whichever is earlier. Open-label TEAE observation period is defined as time from first open-label study treatment administration to last open-label study treatment administration +70 days.

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

End point timeframe:

Baseline to week 32 (End of Study)

| End point values                               | Placebo in DBTP | Alirocumab 150 mg SC Q2W in DBTP | Alirocumab 150 mg SC Q2W in OLTP |  |
|--|-----------------|----------------------------------|----------------------------------|--|
| Subject group type                             | Reporting group | Reporting group                  | Subject analysis set             |  |
| Number of subjects analysed                    | 24              | 45                               | 69                               |  |
| Units: Subjects                                |                 |                                  |                                  |  |
| Subjects with any TEAE                         | 12              | 20                               | 24                               |  |
| Subjects with TEAE Serious Adverse Event (SAE) | 0               | 0                                | 1                                |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) to end of study (Day 225)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP |
|-----------------------|---|

Reporting group description:

Participants received matching placebo subcutaneously (SC) every 2 weeks (Q2W) from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all participants received open-label alirocumab SC Q2W

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Alirocumab 150 Q2W in DBTP and OLTP |
|-----------------------|-------------------------------------|

Reporting group description:

Participants in this arm received alirocumab 150 milligrams (mg) SC Q2W from baseline (Day 1) through Week 10 during the double-blind treatment period. Starting at Week 12, and continuing through Week 22, all participants received open-label alirocumab SC Q2W

| <b>Serious adverse events</b>                     | Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP | Alirocumab 150 Q2W in DBTP and OLTP |  |
|---|---|-------------------------------------|--|
| Total subjects affected by serious adverse events |   |                                     |  |
| subjects affected / exposed                       | 0 / 24 (0.00%)  | 1 / 45 (2.22%)                      |  |
| number of deaths (all causes)                     | 0   | 0                                   |  |
| number of deaths resulting from adverse events    |   |                                     |  |
| Musculoskeletal and connective tissue disorders   |   |                                     |  |
| Arthralgia  |   |                                     |  |
| subjects affected / exposed                       | 0 / 24 (0.00%)  | 1 / 45 (2.22%)                      |  |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 1                               |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                               |  |

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

| <b>Non-serious adverse events</b>                     | Placebo SC Q2W in DBTP and Alirocumab 150 mg SC Q2W in OLTP | Alirocumab 150 Q2W in DBTP and OLTP |  |
|---|---|-------------------------------------|--|
| Total subjects affected by non-serious adverse events |   |                                     |  |
| subjects affected / exposed                           | 6 / 24 (25.00%)   | 14 / 45 (31.11%)                    |  |

|   |  |   |  |
|---|--|---|--|
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 2 / 24 (8.33%)<br>10                           | 3 / 45 (6.67%)<br>3                             |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 24 (0.00%)<br>0                            | 4 / 45 (8.89%)<br>4                             |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)               | 2 / 24 (8.33%)<br>2<br><br>0 / 24 (0.00%)<br>0 | 0 / 45 (0.00%)<br>0<br><br>3 / 45 (6.67%)<br>3  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 24 (4.17%)<br>1<br><br>2 / 24 (8.33%)<br>3 | 5 / 45 (11.11%)<br>7<br><br>2 / 45 (4.44%)<br>2 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 29 March 2017   | Refining diagnostic criteria; adding additional assessments; sample size adjustment in statistical methods; correct inconsistencies and make additional editorial changes                      |
| 11 July 2017    | Added exclusion criteria; extended treatment emergent AE period; clarified text and added definitions; added an assessment for hepatitis C and process instructions; edits and clarifications. |
| 04 January 2019 | Increased sample size; revised ITT population definition   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported