# Clinical trial results:
# A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO EVALUATE THE EFFECT OF 300 MG OF INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HeFH) AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)

## Summary

| | |
|---|---|
| EudraCT number | 2017-002472-30 |
| Trial protocol | GB ES CZ SE DK |
| Global end of trial date | 27 August 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 September 2020 |
| First version publication date | 11 September 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MDCO-PCS-17-03 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03397121 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | The Medicines Company |
| Sponsor organisation address | 8 Sylvan Way, Parsippany, United States, NJ 07054 |
| Public contact | Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com |
| Scientific contact | Global Health Science Center, The Medicines Company, +1 9732906000, medical.information@themedco.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 August 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of inclisiran treatment on:
•LDL-C levels at Day 510
•Time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy:

All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDL-C lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo.

Evidence for comparator:

Use of placebo is consistent with other investigational lipid lowering therapy Phase III designs, including the statins and the monoclonal antibody PCSK9 inhibitors. All subjects participating must be on and maintain maximally tolerated statin therapy and/or other LDL-C lowering therapies such as ezetimibe in addition to receiving inclisiran or placebo. The use of placebo in this type of study is consistent with EU guidance on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3).

| | |
|---|---|
| Actual start date of recruitment | 01 November 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Ethical reason |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 38 |
| Country: Number of subjects enrolled | Spain: 84 |
| Country: Number of subjects enrolled | Sweden: 34 |
| Country: Number of subjects enrolled | Czech Republic: 12 |
| Country: Number of subjects enrolled | Denmark: 49 |
| Country: Number of subjects enrolled | Canada: 23 |
| Country: Number of subjects enrolled | South Africa: 177 |
| Country: Number of subjects enrolled | United States: 65 |
| Worldwide total number of subjects | 482 |
| EEA total number of subjects | 217 |

Notes:

| 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) | 374 |
| From 65 to 84 years | 108 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Not applicable

### Pre-assignment

Screening details:

Screening occurred prior to randomization and consisted of confirming eligibility and collecting Baseline assessments. Subjects enrolled must have fasting triglyceride <4.52 mmol/L (<400 mg/dL) and serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 482 |
| Number of subjects completed | 482 |

### Period 1

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

Blinding implementation details:

Not applicable

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Inclisiran |

Arm description:

Inclisiran sodium 300 milligrams

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Inclisiran |
| Investigational medicinal product code | ALN-60212 |
| Other name | |
| Pharmaceutical forms | Solution for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months.
Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo

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

Dosage and administration details:

Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.

Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).

| **Number of subjects in period 1** | Inclisiran | Placebo |
|---|---|---|
| Started | 242 | 240 |
| Completed | 235 | 231 |
| Not completed | 7 | 9 |
| Initiation of protocol-prohibited PCSK9 inhibitor | - | 1 |
| Consent withdrawn by subject | - | 4 |
| death | 1 | 1 |
| Not specified | 5 | 1 |
| Lost to follow-up | 1 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Inclisiran |
| Reporting group description: | |
| Inclisiran sodium 300 milligrams | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |

| Reporting group values | Inclisiran | Placebo | Total |
|---|---|---|---|
| Number of subjects | 242 | 240 | 482 |
| Age categorical | | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 189 | 185 | 374 |
| Adults (65 - 74 years) | 45 | 48 | 93 |
| Adults (75+ years) | 8 | 7 | 15 |
| Age continuous | | | |
| Age | | | |
| Units: years | | | |
| arithmetic mean | 54.4 | 55.0 | |
| standard deviation | ± 12.48 | ± 12.48 | - |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 130 | 125 | 255 |
| Male | 112 | 115 | 227 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Inclisiran |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months.<br>Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.<br>Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection). | |

| Reporting group values | Inclisiran | Placebo | |
|---|---|---|---|
| Number of subjects | 242 | 240 | |
| Age categorical | | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 189 | 185 | |

| | | | |
|---|---|---|---|
| Adults (65 - 74 years) | 45 | 48 | |
| Adults (75+ years) | 8 | 7 | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Age | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 130 | 125 | |
| Male | 112 | 115 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Inclisiran |
| Reporting group description: | |
| Inclisiran sodium 300 milligrams | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |
| Subject analysis set title | Inclisiran |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months.<br>Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.<br>Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection). | |

### Primary: Percentage Change In LDL-C From Baseline To Day 510

| | |
|---|---|
| End point title | Percentage Change In LDL-C From Baseline To Day 510 |
| End point description: | |
| % change in LDL-C to Day 510 | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to Day 510 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: Percentage change | | | | |
| least squares mean (confidence interval 95%) | -41.15 (-44.52 to -37.77) | 8.37 (3.96 to 12.77) | -41.15 (-44.52 to -37.77) | 8.37 (3.96 to 12.77) |

### Statistical analyses

| Statistical analysis title | Percentage Change In LDL-C From Baseline - Day 510 |
|---|---|
| Statistical analysis description: | |
| Difference in the percentage change in LDL-C from baseline to Day 510 between inclisiran and placebo arms | |
| Comparison groups | Inclisiran v Placebo v Inclisiran v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 964 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -49.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -55.04 |
| upper limit | -43.99 |

## Primary: Time-adjusted Percent Change in LDL-C From Baseline After Day 90 and up to Day 540

| | |
|---|---|
| End point title | Time-adjusted Percent Change in LDL-C From Baseline After Day 90 and up to Day 540 |
| End point description: | |
| Time adjusted change in LDL-C | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Day 90 to Day 540 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: Percentage change | | | | |
| least squares mean (confidence interval 95%) | -38.08 (-41.03 to -35.14) | 6.22 (3.26 to 9.17) | -38.08 (-41.03 to -35.14) | 6.22 (3.26 to 9.17) |

## Statistical analyses

| Statistical analysis title | Percentage Change In LDL-C From Day 90 to Day 540 |
|---|---|
| Statistical analysis description: | |
| Difference in time-adjusted percentage change in LDL-C Levels From Baseline After Day 90 and up to Day 540 between inclisiran and placebo arms | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -44.03 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -48.48 |
| upper limit | -40.12 |

## Secondary: Absolute Change in LDL-C From Baseline to Day 510

| | |
|---|---|
| End point title | Absolute Change in LDL-C From Baseline to Day 510 |
| End point description:<br>Absolute change in LDL-C | |
| End point type | Secondary |
| End point timeframe:<br>Baseline to Day 510 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | -58.95 (-64.75 to -53.15) | 9.94 (4.10 to 15.78) | -58.95 (-64.75 to -53.15) | 9.94 (4.10 to 15.78) |

### Statistical analyses

| Statistical analysis title | Absolute Change in LDL-C From Baseline To Day 510 |
|---|---|
| Statistical analysis description:<br>Difference in Absolute Change in LDL-C From Baseline To Day 510 between inclisiran and placebo arms | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -68.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -77.11 |
| upper limit | -60.67 |

## Secondary: Time-adjusted Absolute Change in LDL-C From Baseline After Day 90

| **and up to Day 540** | |
|---|---|
| End point title | Time-adjusted Absolute Change in LDL-C From Baseline After Day 90 and up to Day 540 |
| End point description:<br>Time-adjusted absolute change in LDL-C | |
| End point type | Secondary |
| End point timeframe:<br>From Baseline After Day 90 and up to Day 540 | |

| **End point values** | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | -56.58 (-60.98 to -52.17) | 6.17 (1.72 to 10.62) | -56.58 (-60.98 to -52.17) | 6.17 (1.72 to 10.62) |

**Statistical analyses**

| **Statistical analysis title** | Absolute Change in Time-adjusted Change in LDL-C |
|---|---|
| Statistical analysis description:<br>Difference in the change in time-adjusted LDL-C after Day 90 and up to Day 540, between inclisiran and placebo groups | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -62.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -69.01 |
| upper limit | -56.48 |

| **Secondary: Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510** | |
|---|---|
| End point title | Percentage Change in Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) From Baseline to Day 510 |
| End point description:<br>Change in PCSK9 | |
| End point type | Secondary |
| End point timeframe:<br>Baseline to Day 510 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: percentage change | | | | |
| least squares mean (confidence interval 95%) | -60.68 (-64.40 to -56.96) | 17.66 (13.91 to 21.42) | -60.68 (-64.40 to -56.96) | 17.66 (13.91 to 21.42) |

### Statistical analyses

| Statistical analysis title | Percentage change in PCSK9 from Baseline - Day 510 |
|---|---|
| Statistical analysis description: | |
| Difference in percentage change in PCSK9 from baseline to Day 510, between inclisiran and placebo arms | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -78.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -83.65 |
| upper limit | -73.04 |

| Secondary: Percentage Change in Total Cholesterol From Baseline to Day 510 | |
|---|---|
| End point title | Percentage Change in Total Cholesterol From Baseline to Day 510 |
| End point description: | |
| Change in total cholesterol | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Day 510 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: Percentage change | | | | |
| least squares mean (confidence interval 95%) | -25.11 (-27.83 to -22.39) | 6.66 (3.96 to 9.36) | -25.11 (-27.83 to -22.39) | 6.66 (3.96 to 9.36) |

**Statistical analyses**

| Statistical analysis title | Percentage change in Total Cholesterol |
|---|---|
| Statistical analysis description: | |
| Difference in the percentage change in total cholesterol from baseline to Day 510, between inclisiran and placebo arms | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -31.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.59 |
| upper limit | -27.94 |

**Secondary: Percentage Change in Apolipoprotein B (ApoB) From Baseline To Day 510**

| End point title | Percentage Change in Apolipoprotein B (ApoB) From Baseline To Day 510 |
|---|---|
| End point description: | |
| Change in ApoB | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline To Day 510 | |

| End point values | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: Percentage change | | | | |
| least squares mean (confidence interval 95%) | -33.14 (-35.91 to -30.36) | 2.93 (0.14 to 5.71) | -33.14 (-35.91 to -30.36) | 2.93 (0.14 to 5.71) |

## Statistical analyses

| **Statistical analysis title** | Percentage change in Apo B form Baseline - Day 510 |
|---|---|
| Statistical analysis description:<br>Difference in the percentage change in Apolipoprotein B (ApoB) from baseline to Day 510 | |
| Comparison groups | Inclisiran v Placebo |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -36.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.99 |
| upper limit | -32.14 |

## Secondary: Percentage Change in Non-high-density Lipoprotein (HDL)-C From Baseline To Day 510

| End point title | Percentage Change in Non-high-density Lipoprotein (HDL)-C From Baseline To Day 510 |
|---|---|
| End point description:<br>Change in non-HDL-C | |
| End point type | Secondary |
| End point timeframe:<br>Baseline To Day 510 | |

| **End point values** | Inclisiran | Placebo | Inclisiran | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 242 | 240 | 242 | 240 |
| Units: Percentage change | | | | |
| least squares mean (confidence interval 95%) | -34.93 (-38.46 to -31.40) | 7.43 (3.93 to 10.92) | -34.93 (-38.46 to -31.40) | 7.43 (3.93 to 10.92) |

## Statistical analyses

| **Statistical analysis title** | Percentage Change in Non-HDL-C: baseline - Day 510 |
|---|---|
| Statistical analysis description: | |
| Difference in the percentage change in Non-HDL-C from baseline to Day 510, between inclisiran and placebo arms | |
| Comparison groups | Placebo v Inclisiran |
| Number of subjects included in analysis | 482 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -42.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.32 |
| upper limit | -37.4 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 0 to Day 510

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Inclisiran |

Reporting group description:

Inclisiran sodium 300 milligrams (mg) will be administered as a SC injection on Day 1, Day 90 then every 6 months.
Inclisiran: Inclisiran is a small interfering ribonucleic acid (RNA) that inhibits PCSK9 synthesis.

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

Reporting group description:

Placebo will be administered as SC injections of saline solution on Day 1, Day 90 then every 6 months.
Placebo: Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection).

| Serious adverse events | Inclisiran | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 241 (7.47%) | 33 / 240 (13.75%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 241 (0.41%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Hernia | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Major depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device loosening | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematuria | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 241 (0.83%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 4 / 240 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 241 (0.83%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 3 / 240 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastritis erosive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| 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 | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 2 / 240 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective tenosynovitis | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 0 / 240 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 241 (0.41%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelitis | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tick-borne fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound sepsis | | | |
| subjects affected / exposed | 0 / 241 (0.00%) | 1 / 240 (0.42%) | |
| 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 %

| **Non-serious adverse events** | Inclisiran | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 96 / 241 (39.83%) | 67 / 240 (27.92%) | |
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 22 / 241 (9.13%) | 0 / 240 (0.00%) | |
| occurrences (all) | 37 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 17 / 241 (7.05%) | 10 / 240 (4.17%) | |
| occurrences (all) | 19 | 11 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 13 / 241 (5.39%) | 21 / 240 (8.75%) | |
| occurrences (all) | 15 | 24 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 28 / 241 (11.62%) | 20 / 240 (8.33%) | |
| occurrences (all) | 36 | 21 | |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 16 / 241 (6.64%)<br>19 | 16 / 240 (6.67%)<br>22 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 November 2017 | Global Amendment #1<br>Clarifications have been made to the various sections of the protocol synopsis and main body in order to address comments received from an FDA review of the study. These clarification are related to exclusion criterion #3, site training requirements and statistics.<br>Changes made to the Synopsis section to include an update to exclusion criterion #3 and the Statistical Methods – Key Secondary Endpoints Analysis.<br>Changes made to the Protocol Main Body include:<br>Section 4.3-Exclusion Criteria,<br>Section 10.3.2.1-Intent-to-Treat (ITT) Population,<br>Section 10.3.2.2-Modified Intent-to-Treat (mITT) Population,<br>Section 10.3.4-Missing Data Handling,<br>Section 10.4.3-Efficacy Analysis, 10.4.3.1.1-Sensitivity Analysis for Primary Efficacy Endpoints and 10.4.3.2-Secondary Efficacy Endpoint.<br>Changes made to the Appendices included the addition of a new Appendix C, Genetic Informed Consent, which shifted the numbering of subsequent appendices. |
| 08 January 2018 | Global Amendment #2<br>Clarifications made to the protocol main body were included in order to address comments received from the FDA.<br>Changes were made to the following sections:<br>Section 4.4-Withdrawal criteria,<br>Section 6.1-Table 2 Schedule of Assessments (including footnote 7) and<br>Section 7.1.3-Vital Signs. |
| 30 August 2018 | Global Amendment #3<br>Changes were made to the Procedures in Case of Emergency section of the protocol to replace Pharmaceutical Product Development, LLC with The Medicines Company.<br>Changes were made to the following sections to remove the month, year and/or edition associated with the Investigator's Brochure as investigative sites should always refer to the latest edition:<br>Section 1.3 Known and Potential Risks and Benefits<br>Section 16 References |
| 31 January 2019 | Global Amendment # 4<br>Changes have been made to the following sections:<br>- Synopsis, Section 3.1, Section 4.1, Section 6.4, Section 10 to account for actual number of randomized subjects.<br>- Synopsis, Section 2.1, Section 3.3, Section 3.4, Section 7.2.1, Section 10.4.3.1 to account for refinement in the description of time adjusted analyses of LDL-C.<br>- Section 6.1. Table 2. Section 6.4, Section 6.6, Section 6.8, Section 7.1.8.8 to clarify the plan to test for ADA.<br>- Section 6.1. Table 2, Schedule of Assessments to align with Health Authority feedback for wider visit windows.<br>- Section 10.3.2.2., Section 10.4.1., Section 10.4.3 to add to account for the addition of a new analysis set (Full Analysis Set).<br>- Section 10.3.3. Analysis Windows and Baseline to clarify that analysis windows will be defined to maximize the amount of data that are included in the analysis models and that full details will be provided in the Statistical Analysis Plan.<br>- Synopsis, Section 10.3.4, Section 10.4.3.1, Section 10.4.3.1.1. Missing Data Handling to align approach to missing data handling with Health Authority feedback and that details are provided in the Statistical Analysis Plan.<br>- Section 10.4.4.2. Laboratory Tests to add analyses for clinically significant laboratory parameters. |

Notes:

## 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.

Not applicable.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/32197277