



Clinical trial results:

Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-16)

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2020-002757-18 |
| Trial protocol | HU NO DE SI NL GR FR IT PL HR SK CZ |
| Global end of trial date | 27 November 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 07 June 2025 |
| First version publication date | 07 June 2025 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CKJX839C12301 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04652726 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-002214-PIP01-17 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 November 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 November 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy, safety and tolerability of inclisiran in adolescents (aged 12 to <18 years) with heterozygous familial hypercholesterolaemia (HeFH).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 27 January 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Brazil: 10 |
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | Czechia: 5 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Israel: 6 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Jordan: 5 |
| Country: Number of subjects enrolled | Lebanon: 3 |
| Country: Number of subjects enrolled | Malaysia: 1 |
| Country: Number of subjects enrolled | Netherlands: 25 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Russian Federation: 3 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Slovenia: 1 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Türkiye: 7 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects | 141 |
| EEA total number of subjects | 75 |

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) | 141 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized from 51 study centers: ARG (1), BRA (3), CAN (1), CZE (2), FRA (3), DEU (2), GRC (1), HUN (1), ISR (2), ITA (4), JOR (1), LBN (1), MYS (1), NLD (2), NOR (1), POL (2), RUS (2), SVK (1), SVN (1), ZAF (3), ESP(4), CHE (1), TWN (1), TUR (4), GBR (1), USA (5)

Pre-assignment

Screening details:

The study had an approximately 4-week screening/run-in period

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------------|
| Arm title | Part 1- Inclisiran |
|------------------|--------------------|

Arm description:

Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Inclisiran |
| Investigational medicinal product code | KJX839 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Inclisiran sodium 300mg(equivalent to 284mginclisiran) in 1.5 mL solution

| | |
|------------------|------------------|
| Arm title | Part 1 - Placebo |
|------------------|------------------|

Arm description:

Placebo sc injection (given at Day 1, 90 and 270)

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

Dosage and administration details:

Placebo formulation to the active drug formulation

| Number of subjects in period 1 | Part 1- Inclisiran | Part 1 - Placebo |
|--------------------------------|--------------------|------------------|
| Started | 93 | 48 |
| Completed | 91 | 48 |
| Not completed | 2 | 0 |
| Physician decision | 1 | - |
| Participant/guardian decision | 1 | - |

Period 2

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

Arms

| | |
|-----------|-----------------------------|
| Arm title | Part 2 – Inclisiran (Total) |
|-----------|-----------------------------|

Arm description:

Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Inclisiran |
| Investigational medicinal product code | KJX839 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Inclisiran sodium 300mg(equivalent to 284mginclisiran) in 1.5 mLsolution

| Number of subjects in period 2 | Part 2 – Inclisiran (Total) |
|--------------------------------|-----------------------------|
| Started | 139 |
| Completed | 139 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Part 1- Inclisiran |
| Reporting group description: | |
| Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270) | |
| Reporting group title | Part 1 - Placebo |
| Reporting group description: | |
| Placebo sc injection (given at Day 1, 90 and 270) | |

| Reporting group values | Part 1- Inclisiran | Part 1 - Placebo | Total |
|----------------------------|--------------------|------------------|-------|
| Number of subjects | 93 | 48 | 141 |
| Age Categorical | | | |
| Units: participants | | | |
| <=18 years | 93 | 48 | 141 |
| Between 18 and 65 years | 0 | 0 | 0 |
| >=65 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 15.2 | 14.9 | |
| standard deviation | ± 2.02 | ± 1.80 | - |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 51 | 24 | 75 |
| Male | 42 | 24 | 66 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 4 | 0 | 4 |
| Black or African American | 5 | 0 | 5 |
| Other | 4 | 0 | 4 |
| White | 80 | 48 | 128 |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Part 1- Inclisiran |
| Reporting group description: Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270) | |
| Reporting group title | Part 1 - Placebo |
| Reporting group description: Placebo sc injection (given at Day 1, 90 and 270) | |
| Reporting group title | Part 2 – Inclisiran (Total) |
| Reporting group description: Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360 | |

Primary: Percentage change in LDL-C from baseline to Day 330 (Part 1/Year 1)

| | |
|--|---|
| End point title | Percentage change in LDL-C from baseline to Day 330 (Part 1/Year 1) |
| End point description: Percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline to Day 330 (Year 1) | |
| End point type | Primary |
| End point timeframe: Baseline and Day 330 | |

| End point values | Part 1- Inclisiran | Part 1 - Placebo | | |
|--|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: percent change in LDL-C | | | | |
| least squares mean (confidence interval 95%) | -27.14 (-32.04 to -22.24) | 1.40 (-3.97 to 6.78) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -28.54 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.81 |
| upper limit | -21.27 |

Secondary: Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1/Year 1)

| | |
|---|--|
| End point title | Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1/Year 1) |
| End point description: | |
| Time-adjusted percent change in LDL-C (after Day 90 and up to Day 330), calculated as the average of percent changes from baseline to Days 150, 270 and 330 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, after Day 90 up to Day 330 | |

| End point values | Part 1- Inclisiran | Part 1 - Placebo | | |
|--|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: Time-adjusted percent change in LDL-C | | | | |
| least squares mean (confidence interval 95%) | -26.04 (-30.11 to -21.98) | 3.26 (-2.37 to 8.89) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -29.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.24 |
| upper limit | -22.36 |

Secondary: Percent change in non-HDL-C from baseline up to Day 330 (Part 1/Year 1)

| | |
|---|---|
| End point title | Percent change in non-HDL-C from baseline up to Day 330 (Part 1/Year 1) |
| End point description: Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to Day 330. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 330 | |

| End point values | Part 1 - Inclisiran | Part 1 - Placebo | | |
|--|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: Percent change in non-HDL-C | | | | |
| least squares mean (confidence interval 95%) | -25.04 (-29.68 to -20.41) | 1.76 (-3.25 to 6.77) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -26.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.63 |
| upper limit | -19.97 |

Secondary: Percent change in Lp(a) from baseline up to Day 330 (Part 1/Year 1)

| | |
|--|---|
| End point title | Percent change in Lp(a) from baseline up to Day 330 (Part 1/Year 1) |
| End point description: Percentage change in lipoprotein (a) [Lp(a)] from baseline to Day 330. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 330 | |

| End point values | Part 1- Inclisiran | Part 1 - Placebo | | |
|--|------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: Percent change in Lp(a) | | | | |
| least squares mean (confidence interval 95%) | -5.04 (-14.21 to 4.13) | 1.14 (-5.48 to 7.77) | | |

Statistical analyses

| Statistical analysis title | Difference between Inclisiran and Placebo |
|---|---|
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1419 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -6.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.48 |
| upper limit | 5.12 |

Secondary: Percent change in Apo B from baseline up to Day 330 (Part 1/Year 1)

| | |
|------------------------|---|
| End point title | Percent change in Apo B from baseline up to Day 330 (Part 1/Year 1) |
| End point description: | Percentage change in apolipoprotein B (Apo B) from baseline to Day 330. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 330 | |

| End point values | Part 1- Inclisiran | Part 1 - Placebo | | |
|--|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: Percent change in Apo B | | | | |
| least squares mean (confidence interval 95%) | -21.46 (-25.59 to -17.33) | 4.24 (-0.07 to 8.56) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -25.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.68 |
| upper limit | -19.73 |

Secondary: Absolute change in LDL-C from baseline to up Day 330 (Part 1/Year 1)

| | |
|--|--|
| End point title | Absolute change in LDL-C from baseline to up Day 330 (Part 1/Year 1) |
| End point description: | |
| Absolute change in LDL-C from baseline to Day 330. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 330 | |

| | | | | |
|--|---------------------------|------------------------|--|--|
| End point values | Part 1- Inclisiran | Part 1 - Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | -50.54 (-59.22 to -41.86) | -0.55 (-10.48 to 9.38) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -49.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -63.18 |
| upper limit | -36.81 |

Secondary: Percent change in total cholesterol from baseline up to Day 330 (Part 1/Year 1)

| | |
|------------------------|---|
| End point title | Percent change in total cholesterol from baseline up to Day 330 (Part 1/Year 1) |
| End point description: | Percentage change in total cholesterol from baseline to Day 330. |
| End point type | Secondary |
| End point timeframe: | Baseline and Day 330 |

| End point values | Part 1 - Inclisiran | Part 1 - Placebo | | |
|--|---------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 | 48 | | |
| Units: Percent change in total cholesterol | | | | |
| least squares mean (confidence interval 95%) | -18.72 (-22.48 to -14.96) | 0.48 (-3.46 to 4.42) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference between Inclisiran and Placebo |
| Comparison groups | Part 1- Inclisiran v Part 1 - Placebo |
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | -19.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.65 |
| upper limit | -13.75 |

Secondary: Percent change in LDL-C from baseline up to Day 720

| | |
|---|---|
| End point title | Percent change in LDL-C from baseline up to Day 720 |
| End point description: Percentage change in LDL-C from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1 - Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|---|------------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 93 | 139 | 48 | |
| Units: Percent change in LDL-C | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 90 (n=93,48,0) | -23.9 (± 22.14) | 999 (± 999) | -0.1 (± 20.16) | |
| DAY 150 (n=92,48,0) | -32.5 (± 21.47) | 999 (± 999) | 6.4 (± 28.83) | |
| DAY 270 (n=92,48,0) | -19.0 (± 28.31) | 999 (± 999) | 2.1 (± 22.44) | |
| DAY 330 (n=90,48,0) | -27.8 (± 22.95) | 999 (± 999) | 1.5 (± 20.59) | |
| DAY 360 (n=90,48,0) | -26.1 (± 22.71) | 999 (± 999) | 1.5 (± 30.56) | |
| DAY 450 (n=0,0,139) | 999 (± 999) | -24.5 (± 26.45) | 999 (± 999) | |
| DAY 510 (n=0,0,139) | 999 (± 999) | -32.5 (± 22.80) | 999 (± 999) | |
| DAY 630 (n=0,0,139) | 999 (± 999) | -26.5 (± 24.33) | 999 (± 999) | |
| Day 720 (study completion) (n=0,0,139) | 999 (± 999) | -33.7 (± 23.98) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in LDL-C from baseline up to Day 720

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|-----------------|--|
| End point title | Absolute change in LDL-C from baseline up to Day 720 |
|-----------------|--|

End point description:

Absolute change in LDL-C from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|---|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 93 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 90 (n=93,48,0) | -45.4 (± 45.26) | 999 (± 999) | -3.0 (± 35.02) | |
| DAY 150 (n=92,48,0) | -61.0 (± 45.84) | 999 (± 999) | 6.6 (± 46.22) | |
| DAY 270 (n=92,48,0) | -38.4 (± 55.77) | 999 (± 999) | 1.0 (± 36.92) | |
| DAY 330 (n=90,48,0) | -51.9 (± 45.47) | 999 (± 999) | -0.3 (± 38.04) | |
| DAY 360 (n=90,48,0) | -49.0 (± 44.49) | 999 (± 999) | -2.9 (± 51.74) | |
| DAY 450 (n=0,0,139) | 999 (± 999) | -46.3 (± 52.51) | 999 (± 999) | |
| DAY 510 (n=0,0,139) | 999 (± 999) | -60.8 (± 48.88) | 999 (± 999) | |
| DAY 630 (n=0,0,139) | 999 (± 999) | -50.9 (± 50.30) | 999 (± 999) | |
| Day 720 (study completion) (n=0,0,139) | 999 (± 999) | -64.1 (± 53.91) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Apo B from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Percent change in Apo B from baseline up to Day 720 |
|-----------------|---|

End point description:

Percentage change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in Apo B | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -25.1 (± 18.18) | 999 (± 999) | 2.2 (± 20.77) | |
| DAY 330 (n=90, 48, 0) | -21.9 (± 19.51) | 999 (± 999) | 3.9 (± 18.13) | |
| DAY 360 (n=90, 48, 0) | -19.3 (± 21.36) | 999 (± 999) | 1.7 (± 22.70) | |
| DAY 510 (n=0, 0, 138) | 999 (± 999) | -24.5 (± 21.77) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -25.7 (± 21.71) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo B from baseline up to Day 720

| | |
|------------------------|--|
| End point title | Absolute change in Apo B from baseline up to Day 720 |
| End point description: | Absolute change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720. |
| End point type | Secondary |
| End point timeframe: | Baseline, up to Day 720 |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -33.3 (± 28.20) | 999 (± 999) | 0.0 (± 27.38) | |
| DAY 330 (n=90, 48, 0) | -29.2 (± 28.04) | 999 (± 999) | 2.9 (± 23.47) | |
| DAY 360 (n=90, 48, 0) | -26.1 (± 29.59) | 999 (± 999) | -0.6 (± 28.72) | |
| DAY 510 (n=0, 0, 138) | 999 (± 999) | -33.5 (± 32.13) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -35.4 (± 33.83) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Lp(a) from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Percent change in Lp(a) from baseline up to Day 720 |
|-----------------|---|

End point description:

Percentage change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1 - Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|------------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in Lp(a) | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -13.4 (± 22.60) | 999 (± 999) | 5.4 (± 23.96) | |
| DAY 330 (n=90, 48, 0) | -7.2 (± 30.80) | 999 (± 999) | 1.1 (± 24.25) | |
| DAY 360 (n=90, 48, 0) | -9.3 (± 28.44) | 999 (± 999) | 3.6 (± 23.27) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -13.3 (± 28.81) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -4.2 (± 163.74) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Lp(a) from baseline up to Day 720

| | |
|-----------------|--|
| End point title | Absolute change in Lp(a) from baseline up to Day 720 |
|-----------------|--|

End point description:

Absolute change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -12.5 (± 34.73) | 999 (± 999) | 3.2 (± 20.67) | |
| DAY 330 (n=90, 48, 0) | -9.5 (± 33.81) | 999 (± 999) | 5.3 (± 21.55) | |
| DAY 360 (n=90, 48, 0) | -10.2 (± 31.16) | 999 (± 999) | 4.4 (± 22.99) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -10.1 (± 34.98) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -9.0 (± 50.08) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in non-HDL-C from baseline up to Day 720

| | |
|--|---|
| End point title | Percent change in non-HDL-C from baseline up to Day 720 |
| End point description: Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in non-HDL-C | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -29.0 (± 20.15) | 999 (± 999) | 5.1 (± 24.85) | |
| DAY 330 (n=90, 48, 0) | -25.7 (± 21.69) | 999 (± 999) | 1.8 (± 19.43) | |
| DAY 360 (n=90, 48, 0) | -24.0 (± 21.74) | 999 (± 999) | 1.2 (± 27.43) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -29.9 (± 21.60) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -31.0 (± 23.04) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in non-HDL-C from baseline up to Day 720

| | |
|-----------------|--|
| End point title | Absolute change in non-HDL-C from baseline up to Day 720 |
|-----------------|--|

End point description:

Absolute change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1 - Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|------------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -60.2 (± 47.41) | 999 (± 999) | 5.7 (± 47.61) | |
| DAY 330 (n=90, 48, 0) | -52.6 (± 46.93) | 999 (± 999) | 0.5 (± 39.20) | |
| DAY 360 (n=90, 48, 0) | -49.7 (± 46.30) | 999 (± 999) | -3.0 (± 52.75) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -62.0 (± 51.09) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -65.1 (± 56.16) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in total cholesterol from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Percent change in total cholesterol from baseline up to Day 720 |
|-----------------|---|

End point description:

Percentage change in total cholesterol from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in total cholesterol | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -22.6 (± 15.77) | 999 (± 999) | 4.4 (± 20.49) | |
| DAY 330 (n=90, 48, 0) | -19.2 (± 17.77) | 999 (± 999) | 0.6 (± 15.46) | |
| DAY 360 (n=90, 48, 0) | -18.5 (± 17.18) | 999 (± 999) | 0.6 (± 21.81) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -23.0 (± 17.50) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -23.7 (± 18.29) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in total cholesterol from baseline up to Day 720

| | |
|-----------------|--|
| End point title | Absolute change in total cholesterol from baseline up to Day 720 |
|-----------------|--|

End point description:

Absolute change in total cholesterol from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | -59.0 (± 47.79) | 999 (± 999) | 6.6 (± 48.08) | |
| DAY 330 (n=90, 48, 0) | -49.4 (± 47.77) | 999 (± 999) | -0.9 (± 38.48) | |
| DAY 360 (n=90, 48, 0) | -48.2 (± 47.06) | 999 (± 999) | -3.1 (± 52.66) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -59.6 (± 51.06) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -62.3 (± 55.05) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in triglycerides from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Percent change in triglycerides from baseline up to Day 720 |
|-----------------|---|

End point description:

Percentage change in triglycerides from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in triglycerides | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 16.2 (± 78.18) | 999 (± 999) | 2.8 (± 37.44) | |
| DAY 330 (n=90, 48, 0) | 1.8 (± 38.39) | 999 (± 999) | 9.7 (± 43.04) | |
| DAY 360 (n=90, 48, 0) | 1.7 (± 40.03) | 999 (± 999) | 3.8 (± 35.76) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | 3.4 (± 43.08) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 1.9 (± 41.84) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in triglycerides from baseline up to Day 720

| | |
|-----------------|--|
| End point title | Absolute change in triglycerides from baseline up to Day 720 |
|-----------------|--|

End point description:

Absolute change in triglycerides from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|---|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n= 92, 48, 0) | 6.9 (± 64.67) | 999 (± 999) | -4.8 (± 31.53) | |
| DAY 330 (n= 90, 48, 0) | -2.9 (± 35.01) | 999 (± 999) | 3.5 (± 35.55) | |
| DAY 360 (n= 90, 48, 0) | -3.1 (± 38.13) | 999 (± 999) | -1.7 (± 28.47) | |
| DAY 510 (n= 0, 0, 139) | 999 (± 999) | -4.2 (± 34.70) | 999 (± 999) | |
| Day 720 (study completion) (n= 0, 0, 139) | 999 (± 999) | -4.8 (± 36.21) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in HDL-C from baseline up to Day 720

| | |
|------------------------|--|
| End point title | Percent change in HDL-C from baseline up to Day 720 |
| End point description: | Percentage change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720. |
| End point type | Secondary |
| End point timeframe: | Baseline, up to Day 720 |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in HDL-C | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 3.6 (± 18.88) | 999 (± 999) | 3.6 (± 16.49) | |
| DAY 330 (n=90, 48, 0) | 7.4 (± 19.15) | 999 (± 999) | -1.9 (± 16.15) | |
| DAY 360 (n=90, 48, 0) | 4.4 (± 19.54) | 999 (± 999) | 0.9 (± 12.39) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | 6.6 (± 19.84) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 7.4 (± 20.40) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HDL-C from baseline up to Day 720

| | |
|--|--|
| End point title | Absolute change in HDL-C from baseline up to Day 720 |
| End point description: Absolute change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 1.2 (± 10.23) | 999 (± 999) | 0.9 (± 8.07) | |
| DAY 330 (n=90, 48, 0) | 3.2 (± 9.57) | 999 (± 999) | -1.4 (± 7.77) | |
| DAY 360 (n=90, 48, 0) | 1.5 (± 9.59) | 999 (± 999) | -0.1 (± 6.23) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | 2.4 (± 9.32) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 2.8 (± 9.75) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in VLDL-C from baseline up to Day 720

| | |
|---|--|
| End point title | Percent change in VLDL-C from baseline up to Day 720 |
| End point description: Percentage change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--------------------------------------|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in VLDL-C | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 11.8 (± 60.04) | 999 (± 999) | 3.3 (± 38.25) | |
| DAY 330 (n=90, 48, 0) | 0.6 (± 39.00) | 999 (± 999) | 10.0 (± 42.29) | |
| DAY 360 (n=90, 48, 0) | 1.0 (± 40.15) | 999 (± 999) | 4.7 (± 35.65) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | 1.4 (± 41.13) | 999 (± 999) | |

| | | | | |
|--|-------------|---------------|-------------|--|
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 1.9 (± 42.20) | 999 (± 999) | |
|--|-------------|---------------|-------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Absolut change in VLDL-C from baseline up to Day 720

| | |
|---|--|
| End point title | Absolut change in VLDL-C from baseline up to Day 720 |
| End point description: Absolute change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 0.7 (± 10.02) | 999 (± 999) | -0.9 (± 6.37) | |
| DAY 330 (n=90, 48, 0) | -0.7 (± 7.04) | 999 (± 999) | 0.8 (± 7.07) | |
| DAY 360 (n=90, 48, 0) | -0.7 (± 7.63) | 999 (± 999) | -0.2 (± 5.66) | |
| DAY 510 (n=0, 0, 139) | 999 (± 999) | -1.2 (± 6.90) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | -1.0 (± 7.40) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo A1 from baseline up to Day 720

| | |
|--|---|
| End point title | Absolute change in Apo A1 from baseline up to Day 720 |
| End point description: Absolute change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 3.3 (± 21.76) | 999 (± 999) | 0.0 (± 17.72) | |
| DAY 330 (n=90, 48, 0) | 6.1 (± 21.16) | 999 (± 999) | -2.8 (± 14.24) | |
| DAY 360 (n=90, 48, 0) | 2.7 (± 21.87) | 999 (± 999) | -2.6 (± 13.89) | |
| DAY 510 (n=0, 0, 138) | 999 (± 999) | 7.5 (± 22.24) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 5.4 (± 21.61) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Apo A1 from baseline up to Day 720

| | |
|--|--|
| End point title | Percent change in Apo A1 from baseline up to Day 720 |
| End point description: | |
| Percentage change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, up to Day 720 | |

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 92 | 139 | 48 | |
| Units: Percent change in Apo A1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 150 (n=92, 48, 0) | 3.7 (± 15.40) | 999 (± 999) | 0.4 (± 13.22) | |
| DAY 330 (n=90, 48, 0) | 5.2 (± 14.49) | 999 (± 999) | -1.5 (± 10.58) | |
| DAY 360 (n=90, 48, 0) | 3.0 (± 15.12) | 999 (± 999) | -1.5 (± 9.98) | |
| DAY 510 (n=0, 0, 138) | 999 (± 999) | 6.3 (± 16.19) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 139) | 999 (± 999) | 4.9 (± 15.56) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in PCSK9 from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Percent change in PCSK9 from baseline up to Day 720 |
|-----------------|---|

End point description:

Percentage change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1 - Inclisiran | Part 2 - Inclisiran (Total) | Part 1 - Placebo | |
|--|------------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 90 | 136 | 48 | |
| Units: Percent change in PCSK9 | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 90 (n=89, 47, 0) | -67.8 (± 15.17) | 999 (± 999) | 11.6 (± 46.61) | |
| DAY 150 (n=90, 47, 0) | -72.3 (± 11.37) | 999 (± 999) | 3.8 (± 36.95) | |
| DAY 330 (n=89, 47, 0) | -72.9 (± 12.12) | 999 (± 999) | 4.8 (± 34.50) | |
| DAY 360 (n=89, 48, 0) | -72.0 (± 10.47) | 999 (± 999) | 11.7 (± 57.77) | |
| DAY 510 (n=0, 0, 136) | 999 (± 999) | -74.3 (± 10.46) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 136) | 999 (± 999) | -71.6 (± 13.42) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolut change in PCSK9 from baseline up to Day 720

| | |
|-----------------|---|
| End point title | Absolut change in PCSK9 from baseline up to Day 720 |
|-----------------|---|

End point description:

Absolute change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.

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

End point timeframe:

Baseline, up to Day 720

| End point values | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo | |
|--|-----------------------|-----------------------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 90 | 136 | 48 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| DAY 90 (n=89, 47, 0) | -259.6 (± 121.5) | 999 (± 999) | 2.1 (± 223.16) | |
| DAY 150 (n=90, 47, 0) | -274.8 (± 116.2) | 999 (± 999) | -27.7 (± 210.44) | |
| DAY 330 (n=89, 47, 0) | -278.2 (± 119.8) | 999 (± 999) | -23.9 (± 210.85) | |
| DAY 360 (n=89, 48, 0) | -275.4 (± 117.2) | 999 (± 999) | -9.1 (± 245.36) | |
| DAY 510 (n=0, 0, 136) | 999 (± 999) | -288.1 (± 156.9) | 999 (± 999) | |
| Day 720 (study completion) (n=0, 0, 136) | 999 (± 999) | -279.5 (± 159.2) | 999 (± 999) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 90 days post treatment or 30 days after last study visit, whichever was longer, up to a maximum duration of approximately 2 years.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 27.1 |

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Part 1- Inclisiran |
|-----------------------|--------------------|

Reporting group description:

Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)

| | |
|-----------------------|-----------------------------|
| Reporting group title | Part 2 – Inclisiran (Total) |
|-----------------------|-----------------------------|

Reporting group description:

Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360

| | |
|-----------------------|------------------|
| Reporting group title | Part 1 - Placebo |
|-----------------------|------------------|

Reporting group description:

Placebo sc injection (given at Day 1, 90 and 270)

| Serious adverse events | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo |
|---|--------------------|-----------------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 93 (3.23%) | 6 / 139 (4.32%) | 1 / 48 (2.08%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|---|----------------|-----------------|----------------|
| Varicose vein | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 0 / 139 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Status migrainosus | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 139 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | 1 / 139 (0.72%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Dengue fever | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | 0 / 139 (0.00%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Non-serious adverse events | Part 1- Inclisiran | Part 2 – Inclisiran (Total) | Part 1 - Placebo |
|--|--|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 57 / 93 (61.29%) | 52 / 139 (37.41%) | 29 / 48 (60.42%) |
| Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 1 / 139 (0.72%) 1 | 1 / 48 (2.08%) 1 |
| Nervous system disorders Migraine subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 12 / 93 (12.90%) 14 5 / 93 (5.38%) 5 | 2 / 139 (1.44%) 2 6 / 139 (4.32%) 8 1 / 139 (0.72%) 1 | 0 / 48 (0.00%) 0 3 / 48 (6.25%) 3 0 / 48 (0.00%) 0 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Injection site reaction subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 4 / 93 (4.30%) 5 4 / 93 (4.30%) 7 8 / 93 (8.60%) 10 0 / 93 (0.00%) 0 | 0 / 139 (0.00%) 0 2 / 139 (1.44%) 2 4 / 139 (2.88%) 7 5 / 139 (3.60%) 5 0 / 139 (0.00%) 0 | 1 / 48 (2.08%) 2 3 / 48 (6.25%) 5 2 / 48 (4.17%) 2 1 / 48 (2.08%) 2 2 / 48 (4.17%) 2 |
| Gastrointestinal disorders | | | |

| | | | |
|---|------------------------|-------------------------|------------------------|
| Vomiting subjects affected / exposed occurrences (all) | 5 / 93 (5.38%) 8 | 0 / 139 (0.00%) 0 | 1 / 48 (2.08%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 | 4 / 139 (2.88%) 4 | 1 / 48 (2.08%) 2 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 93 (3.23%) 3 | 6 / 139 (4.32%) 6 | 2 / 48 (4.17%) 2 |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 17 / 93 (18.28%) 17 | 7 / 139 (5.04%) 7 | 12 / 48 (25.00%) 12 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 | 3 / 139 (2.16%) 4 | 1 / 48 (2.08%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 10 / 93 (10.75%) 11 | 11 / 139 (7.91%) 11 | 6 / 48 (12.50%) 8 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 13 / 93 (13.98%) 14 | 14 / 139 (10.07%) 18 | 9 / 48 (18.75%) 11 |
| Pharyngitis subjects affected / exposed occurrences (all) | 4 / 93 (4.30%) 4 | 1 / 139 (0.72%) 3 | 2 / 48 (4.17%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 93 (6.45%) 10 | 4 / 139 (2.88%) 5 | 2 / 48 (4.17%) 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 28 October 2022 | <p>The purpose of Amendment 1 was to reduce the sample size of the study from approximately 150 participants to a minimum of 102 participants. The revised sample size was based on a careful review of all existing evidence, including new important data available, i.e., the meanwhile well-established, favorable efficacy and safety profile of inclisiran in adults, the comprehensive, supportive non-clinical studies, new re-assuring study results in pediatric patients for drugs with a similar (i.e., PCSK9-directed) mechanism of action, and positive experience with inclisiran in adolescents from two ongoing studies.</p> <p>The revised sample size of at least 102 participants provides more than 90% power to assess the primary efficacy endpoint, under conservative assumptions of a 30% between-group difference and standard deviations of 30/40% for the inclisiran and placebo groups.</p> <p>However, the actual enrollment was 141 participants, which further increased the statistical power for the primary efficacy endpoint and contributed additional safety data.</p> |
| 17 February 2023 | <p>The purpose of Amendment 2 was to add an interim analysis (IA) for the PK data collected on Day 1.</p> |

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: