# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of ISIS 304801 Administered Subcutaneously to Patients with Hypertriglyceridemia

## Summary

| | |
|---|---|
| EudraCT number | 2014-003434-93 |
| Trial protocol | DE NL GB |
| Global end of trial date | 24 January 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 October 2022 |
| First version publication date | 22 October 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | ISIS-304801-CS16 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02300233 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Ionis Pharmaceuticals, Inc. |
| Sponsor organisation address | 2855 Gazelle Court, Carlsbad, CA, United States, 92010 |
| Public contact | Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com |
| Scientific contact | Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.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 | 24 January 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of volanesorsen given for 26 weeks in subjects with Hypertriglyceridemia.

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 | 05 February 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Germany: 22 |
| Country: Number of subjects enrolled | United States: 50 |
| Country: Number of subjects enrolled | Canada: 21 |
| Country: Number of subjects enrolled | France: 8 |
| Worldwide total number of subjects | 113 |
| EEA total number of subjects | 42 |

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 | 0 |

| | |
|---|---|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 101 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 114 subjects were randomised at multiple study centres worldwide.

### Pre-assignment

Screening details:

114 subjects were randomised, and 113 received study drug. One subject was randomised, but discontinued before dosing. The study included a ≤ 8-week screening period (including a diet-stabilization period), a 26-week treatment period, and a 13-week-post-treatment evaluation period.

### Period 1

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

### Arms

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

Arm description:

Volanesorsen-matching placebo administered subcutaneously once-weekly for 26 weeks.

| | |
|---|---|
| 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:

Volanesorsen-matching placebo administered subcutaneously once-weekly for 26 weeks.

| | |
|---|---|
| **Arm title** | Volanesorsen 300 mg Weekly |

Arm description:

Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Volanesorsen |
| Investigational medicinal product code | |
| Other name | ISIS 304801, ApoC-III, Approach, IONIS-APOCIIIRx |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks.

| | |
|---|---|
| **Arm title** | Volanesorsen 300 mg Biweekly, Post Week 13 |

Arm description:

Volanesorsen 300 mg administered subcutaneously once-weekly for 13 weeks, then bi-weekly for 13 weeks.

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

| | |
|---|---|
| Investigational medicinal product name | Volanesorsen |
| Investigational medicinal product code | |
| Other name | ISIS 304801, ApoC-III, Approach, IONIS-APOCIIIRx |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Volanesorsen 300 mg administered subcutaneously once-weekly for 13 weeks, then bi-weekly for 13 weeks.

| **Number of subjects in period 1** | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 |
|---|---|---|---|
| Started | 38 | 25 | 50 |
| Completed | 34 | 24 | 27 |
| Not completed | 4 | 1 | 23 |
| Consent withdrawn by subject | 1 | - | 3 |
| Investigator Judgement | - | - | 1 |
| Reason Not Specified | - | - | 5 |
| Adverse Event or Serious Adverse Event | 3 | 1 | 14 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Volanesorsen-matching placebo administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Weekly |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Biweekly, Post Week 13 |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 13 weeks, then bi-weekly for 13 weeks. | |

| Reporting group values | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 |
|---|---|---|---|
| Number of subjects | 38 | 25 | 50 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53 | 50 | 51 |
| standard deviation | ± 10 | ± 9 | ± 11 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 5 | 14 |
| Male | 30 | 20 | 36 |
| Race | | | |
| Units: Subjects | | | |
| White | 33 | 25 | 47 |
| Asian | 3 | 0 | 1 |
| American Indian or Alaskan Native | 0 | 0 | 1 |
| Other Race | 1 | 0 | 1 |
| Multiple | 1 | 0 | 0 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 0 |
| Not Hispanic or Latino | 37 | 24 | 50 |
| Fasting Triglycerides | | | |
| Units: milligrams per decilitre (mg/dL) | | | |
| arithmetic mean | 1414 | 1046 | 1251 |
| standard deviation | ± 1253 | ± 560 | ± 838 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 113 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br> | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 27<br>86 | | |
| Race<br>Units: Subjects | | | |
| White<br>Asian<br>American Indian or Alaskan Native<br>Other Race<br>Multiple | 105<br>4<br>1<br>2<br>1 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino<br>Not Hispanic or Latino | 2<br>111 | | |
| Fasting Triglycerides<br>Units: milligrams per decilitre (mg/dL)<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | Volanesorsen Total |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks; or once-weekly for 13 weeks, then bi-weekly for 13 weeks.

| **Reporting group values** | Volanesorsen Total | | |
|---|---|---|---|
| Number of subjects | 75 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>50<br>± 10 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 19<br>56 | | |
| Race<br>Units: Subjects | | | |
| White<br>Asian<br>American Indian or Alaskan Native<br>Other Race | 72<br>1<br>1<br>1 | | |

| | | | |
|---|---|---|---|
| Multiple | 0 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | | |
| Not Hispanic or Latino | 74 | | |
| Fasting Triglycerides<br>Units: milligrams per decilitre (mg/dL) | | | |
| arithmetic mean | 1183 | | |
| standard deviation | ± 759 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Volanesorsen-matching placebo administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Weekly |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Biweekly, Post Week 13 |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 13 weeks, then bi-weekly for 13 weeks. | |
| Subject analysis set title | Volanesorsen Total |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks; or once-weekly for 13 weeks, then bi-weekly for 13 weeks. | |

### Primary: Percent Change in Fasting Triglycerides (TG) From Baseline to Month 3

| | |
|---|---|
| End point title | Percent Change in Fasting Triglycerides (TG) From Baseline to Month 3[1] |
| End point description: | |
| The full analysis set (FAS) included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline to 3 months | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was reported for "Volanesorsen Total" arm group (N=75) which is inclusive of "Volanesorsen 300 mg Weekly" (N=25) and "Volanesorsen 300 mg Biweekly, Post Week 13" (N=50) arm groups.

| End point values | Placebo | Volanesorsen Total | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 38 | 75 | | |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | -0.9 (-13.9 to 12.2) | -71.2 (-79.3 to -63.2) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Placebo vs Volanesorsen Total |
| Comparison groups | Placebo v Volanesorsen Total |

| | |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in Least Squares Mean (LSM) |
| Point estimate | -70.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -85.4 |
| upper limit | -55.3 |

## Secondary: Absolute Change in Fasting TG From Baseline to Month 3

| | |
|---|---|
| End point title | Absolute Change in Fasting TG From Baseline to Month 3[2] |

End point description:

The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. Volanesorsen 300 mg biweekly group includes subjects who received weekly dosing in first 13 weeks, and then bi-weekly for 13 weeks. For month 3 assessments, the results were combined since all subjects were on weekly dosing. And for month 6 assessments, the results were split to show the results in each dosing group.

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

End point timeframe:

Baseline to 3 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for "Volanesorsen Total" arm group (N=75) which is inclusive of "Volanesorsen 300 mg Weekly" (N=25) and "Volanesorsen 300 mg Biweekly, Post Week 13" (N=50) arm groups.

| **End point values** | Placebo | Volanesorsen Total | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 38 | 75 | | |
| Units: mg/dL | | | | |
| least squares mean (confidence interval 95%) | 74 (-138 to 285) | -869 (-1018 to -720) | | |

### Statistical analyses

| **Statistical analysis title** | Placebo vs Volanesorsen Total |
|---|---|
| Comparison groups | Placebo v Volanesorsen Total |

| | |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LSM |
| Point estimate | -943 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1197 |
| upper limit | -689 |

## Secondary: Treatment Response Rate Defined as Subjects With Fasting TG ≥ 40% Reduction From Baseline at Month 3

| | |
|---|---|
| End point title | Treatment Response Rate Defined as Subjects With Fasting TG ≥ 40% Reduction From Baseline at Month 3[3] |

End point description:

The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment.

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

End point timeframe:

Baseline to 3 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for "Volanesorsen Total" arm group (N=75) which is inclusive of "Volanesorsen 300 mg Weekly" (N=25) and "Volanesorsen 300 mg Biweekly, Post Week 13" (N=50) arm groups.

| End point values | Placebo | Volanesorsen Total | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 38 | 75 | | |
| Units: Subjects | 5 | 65 | | |

## Statistical analyses

| Statistical analysis title | Placebo vs Volanesorsen Total |
|---|---|
| Comparison groups | Placebo v Volanesorsen Total |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 96.02 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.71 |
| upper limit | 467.79 |

## Secondary: Percent Change in High-density Lipoprotein-cholesterol (HDL-C) From Baseline

| | |
|---|---|
| End point title | Percent Change in High-density Lipoprotein-cholesterol (HDL-C) From Baseline[4] |

End point description:

The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment.

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

End point timeframe:

Baseline to 3 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for "Volanesorsen Total" arm group (N=75) which is inclusive of "Volanesorsen 300 mg Weekly" (N=25) and "Volanesorsen 300 mg Biweekly, Post Week 13" (N=50) arm groups.

| End point values | Placebo | Volanesorsen Total | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 38 | 75 | | |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | 4.4 (-5.2 to 14.0) | 61.2 (54.2 to 68.3) | | |

### Statistical analyses

| Statistical analysis title | Placebo vs Volanesorsen Total |
|---|---|
| Comparison groups | Placebo v Volanesorsen Total |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Difference in LSM |
| Point estimate | 56.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 45.1 |
| upper limit | 68.6 |

## Secondary: Treatment Response Rate Defined as Subjects With Fasting TG < 150 mg/dL Reduction From Baseline at Month 3

| End point title | Treatment Response Rate Defined as Subjects With Fasting TG < 150 mg/dL Reduction From Baseline at Month 3[5] |
|---|---|

End point description:

The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment.

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

End point timeframe:

Baseline to 3 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for "Volanesorsen Total" arm group (N=75) which is inclusive of "Volanesorsen 300 mg Weekly" (N=25) and "Volanesorsen 300 mg Biweekly, Post Week 13" (N=50) arm groups.

| **End point values** | Placebo | Volanesorsen Total | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 38 | 75 | | |
| Units: subjects | 0 | 11 | | |

### Statistical analyses

| **Statistical analysis title** | Placebo vs Volanesorsen Total |
|---|---|
| Comparison groups | Placebo v Volanesorsen Total |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0474 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 14.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 215.88 |

## Secondary: Change From Baseline in Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR)

| End point title | Change From Baseline in Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR) |
|---|---|

End point description:

HOMA-IR was calculated using the following formula: Fasting insulin micro-international units per millimetre (µIU/mL) x fasting glucose [mg/dL]/405. A negative change from baseline indicates improvement; a positive change from baseline indicates worsening. The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. Number analysed "n" indicates the number of subjects evaluated at the given timepoint.

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

End point timeframe:

Baseline to 3 and 6 months

| **End point values** | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 38 | 25 | 50 | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 3 (n=36,24,42) | -0.29 (± 3.12) | 1.53 (± 4.89) | -0.45 (± 4.97) | |
| Month 6 (n=35,24,38) | -0.37 (± 3.18) | 1.54 (± 7.69) | 0.56 (± 2.97) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Glycated Haemoglobin (HbA1c) in Type 2 Diabetes Mellitus (T2DM) Subjects

| End point title | Change From Baseline in Glycated Haemoglobin (HbA1c) in Type 2 Diabetes Mellitus (T2DM) Subjects |
|---|---|

End point description:

The FAS included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. Number analysed "n" indicates the number of T2DM subjects evaluated at given time point.

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

End point timeframe:

Baseline to 3 and 6 months

| **End point values** | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14 | 9 | 21 | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Month 3 (n=13,9,21) | -0.0 (± 0.5) | 0.4 (± 0.6) | 0.1 (± 0.5) | |
| Month 6 (n=12,9,19) | -0.2 (± 0.6) | 0.8 (± 0.9) | 0.3 (± 0.9) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Up to approximately 39 weeks | |
| Adverse event reporting additional description: | |
| The safety set included all randomised subjects who received at least one dose of study drug. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Volanesorsen-matching placebo administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Weekly |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks. | |
| Reporting group title | Volanesorsen 300 mg Biweekly, Post Week 13 |
| Reporting group description: | |
| Volanesorsen 300 mg administered subcutaneously once-weekly for 13 weeks, then bi-weekly for 13 weeks. | |

| Serious adverse events | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 25 (8.00%) | 6 / 50 (12.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 25 (4.00%) | 0 / 50 (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 | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| 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 | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Serum sickness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 25 (0.00%) | 0 / 50 (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 |
| Pancreatitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 25 (4.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis relapsing | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 25 (0.00%) | 0 / 50 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 25 (0.00%) | 0 / 50 (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 |
| Infections and infestations | | | |
| Pancreas infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 25 (0.00%) | 0 / 50 (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 |

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

| **Non-serious adverse events** | Placebo | Volanesorsen 300 mg Weekly | Volanesorsen 300 mg Biweekly, Post Week 13 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 31 / 38 (81.58%) | 24 / 25 (96.00%) | 49 / 50 (98.00%) |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Hot flush | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 23 / 25 (92.00%) | 38 / 50 (76.00%) |
| occurrences (all) | 2 | 198 | 262 |
| Injection site pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 10 / 25 (40.00%) | 29 / 50 (58.00%) |
| occurrences (all) | 2 | 98 | 199 |
| Injection site swelling | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 12 / 25 (48.00%) | 24 / 50 (48.00%) |
| occurrences (all) | 1 | 73 | 105 |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 10 / 25 (40.00%) | 17 / 50 (34.00%) |
| occurrences (all) | 0 | 52 | 106 |
| Injection site discolouration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 12 / 25 (48.00%) | 11 / 50 (22.00%) |
| occurrences (all) | 0 | 44 | 41 |
| Injection site induration | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 7 / 25 (28.00%) | 11 / 50 (22.00%) |
| occurrences (all) | 2 | 18 | 56 |
| Injection site discomfort | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 25 (8.00%) | 11 / 50 (22.00%) |
| occurrences (all) | 1 | 12 | 38 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 25 (8.00%) | 7 / 50 (14.00%) |
| occurrences (all) | 15 | 4 | 11 |
| Injection site bruising | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 25 (4.00%) | 10 / 50 (20.00%) |
| occurrences (all) | 2 | 3 | 34 |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 25 (12.00%) | 6 / 50 (12.00%) |
| occurrences (all) | 0 | 5 | 19 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 2 | 6 | 6 |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 4 / 25 (16.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 0 | 20 | 7 |
| Injection site warmth | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 6 / 50 (12.00%) |
| occurrences (all) | 0 | 26 | 21 |
| Asthenia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 3 / 25 (12.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 2 | 9 | 4 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 0 | 2 | 8 |
| Injection site hypoaesthesia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 25 (4.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 0 | 1 | 9 |
| Injection site inflammation | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 25 (8.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 1 | 20 | 7 |
| Pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 2 | 0 | 2 |
| Injection site mass | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 7 | 9 |
| Injection site oedema | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 0 | 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 0 | 2 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 2 | 4 |
| Investigations | | | |
| Red blood cell sedimentation rate increased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 6 / 25 (24.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 4 | 6 | 6 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 25 (12.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 0 | 3 | 7 |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 25 (12.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 0 | 3 | 4 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 25 (4.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 1 | 2 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 25 (0.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 25 (8.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 1 | 3 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 25 (8.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 5 | 2 | 15 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 2 | 2 | 2 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 8 / 50 (16.00%) |
| occurrences (all) | 2 | 2 | 9 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 3 | 2 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 5 / 25 (20.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 11 | 17 | 6 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 25 (4.00%) | 9 / 50 (18.00%) |
| occurrences (all) | 1 | 1 | 13 |
| Nausea | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 25 (4.00%) | 6 / 50 (12.00%) |
| occurrences (all) | 1 | 2 | 8 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 25 (4.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 1 | 1 | 4 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 25 (0.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 3 | 0 | 2 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 0 | 3 | 2 |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 25 (12.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Actinic keratosis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 25 (0.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 8 | 0 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Albuminuria | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 25 (16.00%) | 8 / 50 (16.00%) |
| occurrences (all) | 7 | 5 | 9 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 7 / 50 (14.00%) |
| occurrences (all) | 0 | 3 | 7 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 25 (8.00%) | 5 / 50 (10.00%) |
| occurrences (all) | 1 | 2 | 5 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 0 | 6 | 5 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 8 / 25 (32.00%) | 4 / 50 (8.00%) |
| occurrences (all) | 6 | 12 | 5 |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 3 | 1 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 2 / 50 (4.00%) |
| occurrences (all) | 2 | 2 | 2 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 25 (0.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 25 (4.00%) | 3 / 50 (6.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Gout | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 25 (4.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 2 | 1 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 25 (8.00%) | 0 / 50 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 07 April 2015 | Changes included: increased the number of randomised subjects to 105; for statistical considerations, modifications were made to the population definition and missing data handling descriptions. |
| 11 April 2016 | Modified the clinical experience safety language to reflect updated blinded safety data from ongoing studies; allowed subjects who screen-failed in ISIS 304801-CS6 to enter ISIS 304801-CS16 (per sponsor approval, in consultation with investigator) if qualified, and for screening and qualification assessments from the ISIS 304801-CS6 study to be used for enrolment into ISIS 304801-CS16; allowed subjects with familial chylomicronaemia syndrome (FCS), as defined in ISIS 304801-CS6 study, and who satisfactorily complete ISIS 304801-CS16, to be considered for eligibility in ISIS 304801-CS7 (i.e., FCS) open-label extension (OLE) study; indicated that, data and safety monitoring board (DSMB) was independent; revised the contraceptive requirements to state that abstinence was only acceptable as true abstinence, i.e., when it was in line with the preferred and usual lifestyle of the subject; increased the frequency of pregnancy testing; added haematology blood draws at Weeks 12, 16, 22 and 25 to more frequently assess platelet counts; allowed blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, and 32 to be conducted by a home healthcare nurse; added language that each time a haematology lab was drawn and sent to the central laboratory for analysis, an additional sample would be collected in parallel and analysed locally, to reduce the occurrence of unreportable haematology results; provided guidance that the length of fasting should preferably not be more than 12 hours; updated platelet monitoring rule language to allow for more frequent monitoring as determined by the sponsor medical monitor in consultation with the investigator; provided guidance on monitoring for insulin, oral antidiabetic medication and glucose; added a safety monitoring rule and guidance for severe hypoglycaemia; clarified guidance on determining relatedness of a suspected unexpected serious adverse event (SUSAR); modified the statistical analyses methods in accordance with regulatory agency requests. |
| 05 May 2016 | Changes included: added language that any case of a platelet count ≤ 50,000/cubic millimetre (mm^3) should be reported in an expedited fashion to the sponsor; added language regarding the frequency of obtaining platelet counts after a study drug dose pause and subsequent rechallenge; added language that any unreportable platelet count result must have been rechecked and determined not to have met a stopping rule before dosing could continue. |

| | |
|---|---|
| 06 June 2016 | Haematology blood draws so that platelet counts (PCs) were measured every 2 weeks (Ws) during treatment (T) period and every 2 Ws for first 6 Ws after last dose (D) of study drug; updated platelet safety monitoring rules; indicated that if there were no reportable PC within 14 days of last PC, investigator (Iv) would contact subject (S) to hold dosing until a new PC was obtained and reviewed; indicated that all PC results would be promptly reviewed by Iv to ensure that C had not met stopping rule and to determine whether rate of decline was suggestive that S could be approaching D pause rule of 75000/mm3 (M); changed platelet D pause/stopping rule from 50000/M to 75000/M and added that when PC returned to ≥100000/M dosing could be continued but at a reduced D frequency of 300mg every 2 Ws or a reduced D of 150mg/W and only if approved by sponsor medical monitor; indicated that in event of any PC less than 25000/M, or a PC less than 50000/M that occurred while S was on dosing at 300mg every 2 Ws or 150mg/W, then dosing of a S with study drug (volanesorsen or placebo) would be stopped permanently; PC would be monitored daily until 2 successive values showed improvement, then monitored every 2-3days until PC was stable; indicated that administration of steroids was recommended for Ss whose PC was less than 25000/M and provided T guidelines for administration of steroids; added a table summarising actions to be taken in event of a low PC; indicated that all Ss would have D frequency reduced to 300mg every 2 Ws or D reduced to 150mg/W after 13 Ws of T (exemptions were Ss who had completed ≥5 months of dosing as of 27 May 2016); added effect of gender on pharmacokinetics (PK) by separate population PK analysis (A) rather than descriptive statistics for a robust assessment and to estimate half-life by separate population PKA rather than non-compartmental analysis. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported