



Clinical trial results:

A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Safety, Tolerability and Pharmacodynamics of ISIS 484137 (ISIS-DGAT2Rx, an Antisense Inhibitor of Diacylglycerol Acyltransferase 2) Administered Once-Weekly for 13 Weeks on Hepatic Steatosis in Adult Patients with Type 2 Diabetes

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-003197-13 |
| Trial protocol | HU |
| Global end of trial date | 28 November 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 04 January 2020 |
| First version publication date | 04 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | ISIS484137-CS2 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03334214 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ionis Pharmaceuticals, Inc. |
| Sponsor organisation address | 2855 Gazelle Court, Carlsbad, United States, CA 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 | 28 November 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are:

1. To evaluate the safety and tolerability of ISIS 484137 250 mg per week subcutaneous (SC) injection in adult subjects with type 2 diabetes mellitus (T2DM)
2. To evaluate the pharmacodynamic effects of ISIS 484137 250 mg per week SC injection on the absolute reduction of liver fat (assessed by magnetic resonance imaging [MRI] proton density fat fraction [PDFF]) in adult subjects with T2DM

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 03 November 2017 |
| 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? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | Canada: 2 |
| Worldwide total number of subjects | 44 |
| 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 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---------------------------|----|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 26 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

44 subjects were randomised at 3 study centres in Canada, Hungary and Poland.

Pre-assignment

Screening details:

A total of 173 subjects were screened for the study and 44 subjects were randomised and received study drug.

Period 1

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

Arms

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

Arm description:

Calculated volume to match active comparator administered subcutaneously once weekly for 13 weeks.

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

Subjects received ISIS 484137 matching-placebo, by subcutaneous (SC) injection, once weekly for 13 weeks.

| | |
|------------------|----------------------|
| Arm title | IONIS DGAT2Rx 250 mg |
|------------------|----------------------|

Arm description:

Single dose of DGAT2Rx administered subcutaneously once weekly for 13 weeks.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | IONIS DGAT2Rx |
| Investigational medicinal product code | ISIS 484137 |
| Other name | ISIS-DGAT2Rx |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received ISIS 484137 250 mg, by SC injection, once weekly for 13 weeks.

| Number of subjects in period 1 | Placebo | IONIS DGAT2Rx 250 mg |
|--|---------|----------------------|
| Started | 15 | 29 |
| Completed | 14 | 25 |
| Not completed | 1 | 4 |
| Ineligibility | - | 1 |
| Voluntary withdrawal | 1 | - |
| Adverse Event or Serious Adverse Event | - | 3 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Calculated volume to match active comparator administered subcutaneously once weekly for 13 weeks. | |
| Reporting group title | IONIS DGAT2Rx 250 mg |
| Reporting group description: | |
| Single dose of DGAT2Rx administered subcutaneously once weekly for 13 weeks. | |

| Reporting group values | Placebo | IONIS DGAT2Rx 250 mg | Total |
|--|---------|----------------------|-------|
| Number of subjects | 15 | 29 | 44 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 63 | 62 | |
| standard deviation | ± 6 | ± 7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 14 | 22 |
| Male | 7 | 15 | 22 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 15 | 29 | 44 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race Units: Subjects | | | |
| White | 15 | 29 | 44 |
| Liver Fat Percentage Units: percentage | | | |
| arithmetic mean | 19.54 | 18.48 | |
| standard deviation | ± 5.68 | ± 6.04 | - |

Subject analysis sets

| | |
|----------------------------|------------------------|
| Subject analysis set title | Placebo (per protocol) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | IONIS DGAT2Rx 250 mg (per protocol) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

| Reporting group values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | |
|---|------------------------|-------------------------------------|--|
| Number of subjects | 12 | 25 | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | ± | ± | |
| Gender categorical Units: Subjects | | | |
| Female Male | | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported | | | |
| Race Units: Subjects | | | |
| White | | | |
| Liver Fat Percentage Units: percentage arithmetic mean standard deviation | 19.77 ± 6.03 | 18.22 ± 6.05 | |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Calculated volume to match active comparator administered subcutaneously once weekly for 13 weeks. | |
| Reporting group title | IONIS DGAT2Rx 250 mg |
| Reporting group description: Single dose of DGAT2Rx administered subcutaneously once weekly for 13 weeks. | |
| Subject analysis set title | Placebo (per protocol) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations. | |
| Subject analysis set title | IONIS DGAT2Rx 250 mg (per protocol) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations. | |

Primary: Percentage of Subjects With Adverse Events That Were Related to Treatment With IONIS DGAT2Rx

| | |
|--|---|
| End point title | Percentage of Subjects With Adverse Events That Were Related to Treatment With IONIS DGAT2Rx ^[1] |
| End point description: An adverse event (AE) is any unfavourable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product. The safety set included all randomised subjects who received at least one dose of study drug. | |
| End point type | Primary |
| End point timeframe: Up to 176 days | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this endpoint.

| End point values | Placebo | IONIS DGAT2Rx 250 mg | | |
|-------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 29 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 13.3 | 48.3 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events, Graded by Severity, That Were Related to Treatment With IONIS DGAT2Rx

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Adverse Events, Graded by Severity, That Were Related to Treatment With IONIS DGAT2Rx ^[2] |
|-----------------|--|

End point description:

AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010. Grades: mild - the event is easily tolerated by the subject and does not affect the subject's usual daily activities; moderate - the event causes the subject more discomfort and interrupts the subject's usual daily activities; severe - the event is incapacitating and causes considerable interference with the subject's usual daily activities. The safety set included all randomised subject who received at least one dose of study drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 176 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed for this endpoint.

| End point values | Placebo | IONIS DGAT2Rx 250 mg | | |
|-------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 29 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Mild | 6.7 | 37.9 | | |
| Moderate | 6.7 | 6.9 | | |
| Severe | 0.0 | 3.4 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Change in Liver Fat Percentage

| | |
|-----------------|---|
| End point title | Absolute Change in Liver Fat Percentage |
|-----------------|---|

End point description:

Absolute change in liver fat percentage as quantified by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) from baseline to post-treatment MRI. The randomised population included all subjects who are randomised into the study regardless of whether they received the study drug. Per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to Week 15

| End point values | Placebo | IONIS DGAT2Rx 250 mg | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) |
|--------------------------------------|-----------------|----------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 15 | 26 | 12 | 25 |
| Units: Liver fat percentage | | | | |
| arithmetic mean (standard deviation) | -0.04 (± 5.82) | -5.37 (± 5.41) | -0.64 (± 6.11) | -5.15 (± 5.40) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg (Randomized Set) |
| Comparison groups | Placebo v IONIS DGAT2Rx 250 mg |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | ANOVA |

| | |
|---|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg (per protocol) |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 |
| Method | ANOVA |

Secondary: Percent Change in Liver Fat Percentage

| | |
|--|--|
| End point title | Percent Change in Liver Fat Percentage |
| End point description: Relative percent change in liver fat percentage from baseline to post-treatment MRI. The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations. | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 15 | |

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|--------------------------------------|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -2.4 (± 28.8) | -25.5 (± 26.5) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.024 |
| Method | ANOVA |

Secondary: Percentage of Subjects With ≥ 30% Relative Reduction in Liver Fat Percentage

| | |
|---|--|
| End point title | Percentage of Subjects With ≥ 30% Relative Reduction in Liver Fat Percentage |
| End point description: Percentage of subjects with ≥ 30% relative reduction in liver fat percentage from baseline to post-treatment. The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations. | |
| End point type | Secondary |
| End point timeframe: Week 15 | |

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|-------------------------------|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 16.7 | 48.0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0774 ^[3] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[3] - The p-value is obtained using Cochran-Mantel-Haenszel (CMH) test stratified by the baseline liver fat stratum (<20%, ≥20%) stratification factor.

Secondary: Percent Change in Plasma Lipoprotein Profile

| | |
|-----------------|--|
| End point title | Percent Change in Plasma Lipoprotein Profile |
|-----------------|--|

End point description:

Percent change in plasma lipoprotein profile (total cholesterol, apolipoprotein B [apoB], high density lipoprotein (HDL), low density lipoprotein cholesterol [LDL-C], non-HDL, triglycerides, and very low density lipoproteins [VLDL]) from baseline to the average of the post-treatment values assessed 1 and 2 weeks after the last dose (Post-Treatment 1 and Post-Treatment 2 visits). The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

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

End point timeframe:

Week 15

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|--------------------------------------|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total cholesterol | -4.4 (± 9.6) | -2.9 (± 14.2) | | |
| apoB | -8.1 (± 9.5) | -6.7 (± 15.3) | | |
| HDL | 1.0 (± 6.3) | 2.2 (± 11.6) | | |
| LDL-C | -8.8 (± 14.9) | -3.8 (± 24.1) | | |
| Non-HDL | -7.1 (± 13.4) | -3.8 (± 18.7) | | |
| Triglycerides | -0.8 (± 20.3) | 2.8 (± 20.1) | | |
| VLDL-C | -0.7 (± 20.3) | 2.0 (± 18.5) | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Total Cholesterol

| | |
|-------------------|--|
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
|-------------------|--|

| | |
|---|---------------|
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.682 |
| Method | ANOVA |

| | |
|---|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Statistical analysis description: apoB | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.716 |
| Method | ANOVA |

| | |
|--|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Statistical analysis description: HDL | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.717 |
| Method | ANOVA |

| | |
|--|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Statistical analysis description: LDL-C | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.463 |
| Method | ANOVA |

| | |
|--|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Statistical analysis description: Non-HDL | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |

| | |
|---|---------------|
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.555 |
| Method | ANOVA |

| | |
|--|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Statistical analysis description: Triglycerides | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.619 |
| Method | ANOVA |

| | |
|---|--|
| Statistical analysis title | Placebo, IONIS DGAT2Rx 250 mg |
| Statistical analysis description: VLDL-C | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.698 |
| Method | ANOVA |

Secondary: Percent Change in Parameters of Insulin Resistance (IR)

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|---|---|
| End point title | Percent Change in Parameters of Insulin Resistance (IR) |
| End point description: Percent change in parameters of IR (fasting plasma glucose [FPG], homeostatic model assessment - insulin resistance [HOMA-IR], and insulin) from baseline to post-treatment. The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations. "n" is the number of subjects with data available for analysis at specified timepoint. | |
| End point type | Secondary |
| End point timeframe: Week 14 | |

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|--------------------------------------|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| FPG (n= 12, 24) | -6.3 (± 23.1) | -6.9 (± 16.1) | | |
| HOMA-IR (n= 12, 24) | -16.9 (± 29.7) | 2.6 (± 46.8) | | |
| Insulin (n= 12, 24) | -10.3 (± 21.7) | 10.1 (± 44.8) | | |

Statistical analyses

| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
|--|--|
| Statistical analysis description: FPG | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.902 |
| Method | ANOVA |

| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
|--|--|
| Statistical analysis description: HOMA-IR | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.267 |
| Method | Van Elteren test |

| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
|--|--|
| Statistical analysis description: Insulin | |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2 |
| Method | Van Elteren test |

Secondary: Absolute Change in Haemoglobin A1C (HbA1C)

| | |
|-----------------|--|
| End point title | Absolute Change in Haemoglobin A1C (HbA1C) |
|-----------------|--|

End point description:

Absolute change in HbA1C from baseline to post-treatment. The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

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

End point timeframe:

Week 14

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|--|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: percentage of total haemoglobin | | | | |
| arithmetic mean (standard deviation) | -0.2 (± 0.7) | -0.2 (± 0.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.933 |
| Method | ANOVA |

Secondary: Percent Change in Liver Volume

| | |
|-----------------|--------------------------------|
| End point title | Percent Change in Liver Volume |
|-----------------|--------------------------------|

End point description:

Assessed from Baseline MRI to Post-Treatment MRI. The per protocol set included all randomised subjects who received at least 10 of the prescribed doses and received the first 4 doses in the first 5 weeks, not missing 3 consecutive weekly doses and having no significant protocol deviations.

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

End point timeframe:

Baseline to Week 15

| End point values | Placebo (per protocol) | IONIS DGAT2Rx 250 mg (per protocol) | | |
|--------------------------------------|------------------------|-------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 25 | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -1.9 (± 7.2) | -6.3 (± 9.8) | | |

Statistical analyses

| Statistical analysis title | Placebo v IONIS DGAT2Rx 250 mg |
|---|--|
| Comparison groups | Placebo (per protocol) v IONIS DGAT2Rx 250 mg (per protocol) |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.183 |
| Method | ANOVA |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 176 days

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 | 21.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Calculated volume to match active comparator administered subcutaneously once weekly for 13 weeks.

| | |
|-----------------------|----------------------|
| Reporting group title | IONIS DGAT2Rx 250 mg |
|-----------------------|----------------------|

Reporting group description:

Single dose of DGAT2Rx administered subcutaneously once weekly for 13 weeks.

| Serious adverse events | Placebo | IONIS DGAT2Rx 250 mg | |
|---|----------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 4 / 29 (13.79%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Nervous system disorders | | | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | IONIS DGAT2Rx 250 mg | |
|---|------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 15 (66.67%) | 20 / 29 (68.97%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |

| | | | |
|--|----------------|------------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Headache | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 4 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 10 / 29 (34.48%) | |
| occurrences (all) | 0 | 45 | |
| Injection site bruising | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 4 / 29 (13.79%) | |
| occurrences (all) | 1 | 18 | |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 5 / 29 (17.24%) | |
| occurrences (all) | 0 | 11 | |
| Injection site pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 4 / 29 (13.79%) | |
| occurrences (all) | 0 | 14 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 4 / 29 (13.79%) | |
| occurrences (all) | 0 | 24 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 2 / 29 (6.90%) | |
| occurrences (all) | 2 | 7 | |
| Oedema peripheral | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 29 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 2 / 29 (6.90%) | |
| occurrences (all) | 3 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 2 / 29 (6.90%) | |
| occurrences (all) | 0 | 2 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Reproductive system and breast disorders | | | |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 2 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 3 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Joint swelling | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 29 (0.00%) 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 4 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 3 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 3 / 29 (10.34%) | |
| occurrences (all) | 1 | 3 | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported