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)

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	1 / 15 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	1	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	1 / 15 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	1	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