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

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 Units: Subjects			

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

Multiple	0		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	74		
Fasting Triglycerides 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