Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Summary

EudraCT number	2014-002421-35
Trial protocol	GB DE IT HU ES
Global end of trial date	28 March 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	ISIS304801-CS6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02211209
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	28 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 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 52 weeks in subjects with Familial Chylomicronemia Syndrome.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2014
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	Canada: 14
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	66
EEA total number of subjects	36

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)	61
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

67 subjects were randomised at 40 study centres in the United States, Canada, Brazil, France, Germany, Israel, Italy, Netherlands, South Africa, Spain, and the United Kingdom.

Pre-assignment

Screening details:

67 subjects were randomised, and 66 received study drug. The study included an 8-week screening period (including a diet-stabilization period), a 52-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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Volanesorsen-matching placebo administered subcutaneously once-weekly for 52 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 52 weeks.

Arm title	Volanesorsen

Arm description:

Volanesorsen 300 mg administered subcutaneously once-weekly for 52 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 52 weeks.

Number of subjects in period 1	Placebo	Volanesorsen
Started	33	33
Completed	32	19
Not completed	1	14
Investigator judgment	-	1
Voluntary withdrawal	1	4
Adverse Event or Serious Adverse Event	-	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Volanesorsen-matching placebo administered subcutaneously once-weekly for 52 weeks.	
Reporting group title	Volanesorsen
Reporting group description:	
Volanesorsen 300 mg administered subcutaneously once-weekly for 52 weeks.	

Reporting group values	Placebo	Volanesorsen	Total
Number of subjects	33	33	66
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46	47	
standard deviation	± 14	± 13	-
Gender categorical Units: Subjects			
Female	19	17	36
Male	14	16	30
Ethnicity Units: Subjects			
Hispanic or Latino	7	7	14
Not Hispanic or Latino	26	26	52
Race Units: Subjects			
White	29	24	53
Asian	4	7	11
Other Race	0	2	2
Fasting Triglycerides Units: milligrams per decilitre (mg/dL)			
arithmetic mean	2152	2267	
standard deviation	± 1153	± 1259	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Volanesorsen-matching placebo administered subcutaneously once-weekly for 52 weeks.	
Reporting group title	Volanesorsen
Reporting group description:	
Volanesorsen 300 mg administered subcutaneously once-weekly for 52 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
End point description:	
The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. The full analysis set 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	

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: percent change				
least squares mean (confidence interval 95%)	17.6 (-4.0 to 39.2)	-76.5 (-97.4 to -55.5)		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Placebo v Volanesorsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-94.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-121.7
upper limit	-66.6

Secondary: Treatment Response Rate Defined as Subjects With Fasting Plasma TG < 750 mg/dL at Month 3

End point title	Treatment Response Rate Defined as Subjects With Fasting Plasma TG < 750 mg/dL at Month 3

End point description:

The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. The full analysis set included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. Data were reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Baseline to 3 months

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	30		
Units: subjects	3	23		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Volanesorsen v Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	186.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.86
upper limit	99999

Notes:

[1] - 99999 indicates that the upper limit of 95% CI was not estimable.

Secondary: Frequency and Severity of Participant-reported Abdominal Pain During the Treatment Period

End point title	Frequency and Severity of Participant-reported Abdominal Pain During the Treatment Period

End point description:

Abdominal pain was measured according to the Bracket electronic patient-reported outcomes (ePRO) assessment. Scores were categorized as follows: no pain (pain score: 0), mild (pain score: 1-3), moderate (pain score: 4-6), or severe (pain score: 7-10). The yearly frequency was calculated as the

number of episodes during the on-treatment period / (last dose date - first dose date + 28) * 365.25. Missing data were imputed by using next observation carried back (NOCB) if there was a subsequent score available. The full analysis set 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 12 months

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: subjects				
No pain	19	18		
Mild	1	4		
Moderate	5	6		
Severe	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Postprandial TG Area Under the Curve (AUC) (0-9h)

End point title	Change From Baseline in Postprandial TG Area Under the Curve (AUC) (0-9h)

End point description:

Subjects had 2 postprandial assessments-one at Baseline (completed at 48 hours prior to first dose) and one at any time between Week 13 and 19; inclusive. Assessment timepoints include from 1-hr before to up to 9 hrs after ingestion of the meal at 1-hour interval. Postprandial AUC results were calculated using a linear trapezoidal rule for each postprandial measure in the subset of participants who had postprandial assessments 0-9 hour results at baseline and the postbaseline between Week 13 to 19. The full analysis set included all subjects who were randomised, received at least one dose of study drug, and had a baseline TG assessment. Data were reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Baseline to an on-treatment assessment between Week 13 and Week 19

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: millimole hours per litre (mmol*h/L)				
arithmetic mean (standard deviation)	36.92 (± 121.54)	-234.77 (± 94.86)		

Statistical analyses

No statistical analyses for this end point

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

End point description:

The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. The full analysis set 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

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: subjects	3	29		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Placebo v Volanesorsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	99.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.75
upper limit	631.06

Secondary: Absolute Change From Baseline in Fasting TG at Month 3

End point title	Absolute Change From Baseline in Fasting TG at Month 3

End point description:

The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. The full analysis set 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

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: mg/dL				
least squares mean (confidence interval 95%)	92 (-301 to 486)	-1712 (-2094 to -1330)		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Placebo v Volanesorsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-1804
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2306
upper limit	-1302
Variability estimate	Standard error of the mean
Dispersion value	251

Secondary: Frequency of the Composite of Episodes of Acute Pancreatitis and Subject-reported Moderate/Severe Abdominal Pain During the Treatment Period

End point title	Frequency of the Composite of Episodes of Acute Pancreatitis and Subject-reported Moderate/Severe Abdominal Pain During the Treatment Period

End point description:

Moderate/severe abdominal pain was defined as having a pain score of 4-10 on the Bracket electronic patient-reported outcomes (ePRO) assessment. Scores were categorized as follows: no pain (pain score: 0), mild (pain score: 1-3), moderate (pain score: 4-6), or severe (pain score: 7-10). The yearly frequency was calculated as the number of episodes during the on-treatment period / (last dose date -

first dose date + 28) * 365.25. The full analysis set 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:

12 months

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: events per subject per year				
arithmetic mean (standard deviation)	2.04 (± 4.28)	2.73 (± 6.57)		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Placebo v Volanesorsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6131
Method	t-test, 2-sided

Secondary: Change From Baseline in Hepatosplenomegaly as Assessed by MRI at Week 52

End point title	Change From Baseline in Hepatosplenomegaly as Assessed by MRI at Week 52

End point description:

The Week 52 endpoint was defined as the average of Week 50 (Day 344)/Week 51 (Day 351) and Week 52 (Day 358) fasting assessments. The full analysis set 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 Week 52

End point values	Placebo	Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: cubic centimetres (cm^3)				
least squares mean (confidence interval 95%)	-25 (-150 to 100)	113 (-43 to 269)		

Statistical analyses

Statistical analysis title	Placebo vs Volanesorsen
Comparison groups	Placebo v Volanesorsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1206
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	138
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36
upper limit	312

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 65 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 52 weeks.	
Reporting group title	Volanesorsen
Reporting group description:	
Volanesorsen 300 mg administered subcutaneously once-weekly for 52 weeks.	

Serious adverse events	Placebo	Volanesorsen	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	7 / 33 (21.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
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	Volanesorsen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 33 (81.82%)	32 / 33 (96.97%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 33 (3.03%)	11 / 33 (33.33%)	
occurrences (all)	1	13	
Haemoglobin decreased			
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Hot flush			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 33 (15.15%)	7 / 33 (21.21%)	
occurrences (all)	8	10	
Hypoaesthesia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Paraesthesia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site erythema			

subjects affected / exposed	1 / 33 (3.03%)	25 / 33 (75.76%)	
occurrences (all)	1	235	
Injection site pain			
subjects affected / exposed	3 / 33 (9.09%)	15 / 33 (45.45%)	
occurrences (all)	25	63	
Fatigue			
subjects affected / exposed	3 / 33 (9.09%)	7 / 33 (21.21%)	
occurrences (all)	3	23	
Injection site swelling			
subjects affected / exposed	2 / 33 (6.06%)	7 / 33 (21.21%)	
occurrences (all)	15	24	
Asthenia			
subjects affected / exposed	3 / 33 (9.09%)	5 / 33 (15.15%)	
occurrences (all)	3	7	
Injection site pruritus			
subjects affected / exposed	0 / 33 (0.00%)	8 / 33 (24.24%)	
occurrences (all)	0	69	
Injection site discolouration			
subjects affected / exposed	0 / 33 (0.00%)	7 / 33 (21.21%)	
occurrences (all)	0	23	
Injection site induration			
subjects affected / exposed	0 / 33 (0.00%)	7 / 33 (21.21%)	
occurrences (all)	0	36	
Injection site bruising			
subjects affected / exposed	0 / 33 (0.00%)	5 / 33 (15.15%)	
occurrences (all)	0	15	
Injection site oedema			
subjects affected / exposed	0 / 33 (0.00%)	5 / 33 (15.15%)	
occurrences (all)	0	19	
Injection site reaction			
subjects affected / exposed	0 / 33 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	15	
Chest pain			
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Influenza like illness			

subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Injection site hypoaesthesia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Injection site pallor			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	37	
Injection site warmth			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	9	
Oedema			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	6	
Injection site dryness			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	13	
Injection site haematoma			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	4	
Injection site urticaria			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	64	
Malaise			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 33 (18.18%)	9 / 33 (27.27%)	
occurrences (all)	9	12	
Nausea			
subjects affected / exposed	2 / 33 (6.06%)	6 / 33 (18.18%)	
occurrences (all)	3	12	
Vomiting			
subjects affected / exposed	3 / 33 (9.09%)	5 / 33 (15.15%)	
occurrences (all)	6	8	
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	5 / 33 (15.15%)	
occurrences (all)	3	11	
Abdominal pain upper			
subjects affected / exposed	4 / 33 (12.12%)	2 / 33 (6.06%)	
occurrences (all)	4	3	
Constipation			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 33 (12.12%)	1 / 33 (3.03%)	
occurrences (all)	6	11	
Epistaxis			
subjects affected / exposed	0 / 33 (0.00%)	5 / 33 (15.15%)	
occurrences (all)	0	7	
Nasal congestion			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	1	2	

Oropharyngeal pain			
subjects affected / exposed	3 / 33 (9.09%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 33 (9.09%)	6 / 33 (18.18%)	
occurrences (all)	3	8	
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)	3 / 33 (9.09%)	
occurrences (all)	4	5	
Petechiae			
subjects affected / exposed	0 / 33 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	1 / 33 (3.03%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Urticaria			
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	6	
Hyperhidrosis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 33 (3.03%)	5 / 33 (15.15%)	
occurrences (all)	1	10	
Back pain			
subjects affected / exposed	4 / 33 (12.12%)	1 / 33 (3.03%)	
occurrences (all)	6	1	
Pain in extremity			
subjects affected / exposed	1 / 33 (3.03%)	4 / 33 (12.12%)	
occurrences (all)	1	5	
Arthralgia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	10	
Neck pain			

subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 33 (21.21%)	5 / 33 (15.15%)	
occurrences (all)	10	8	
Urinary tract infection			
subjects affected / exposed	3 / 33 (9.09%)	2 / 33 (6.06%)	
occurrences (all)	4	4	
Gastroenteritis			
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
Influenza			
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	5	1	
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Viral infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2014	Extended the treatment period from 6 to 12 months; expanded enrolment of subjects with a history of acute pancreatitis to at least 36 of the 50 subjects (72%); incorporated a stratification of subjects by previous history of pancreatitis, replacing the Glybera exposure strata; modified statistical methods for handling missing data and for the primary analysis; added a description of the planned collection and analysis of injection site reactions; removed the exclusion based on screening echocardiogram results; added fundus photography to study procedures to better assess the presence/absence of lipemia retinalis; made minor changes to correct errors and/or to improve the overall clarity of the protocol.
20 November 2015	Updated the approximate anticipated number of subjects that could enrol into the study (approximately 60 subjects); updated the time point for the collection of post-heparin samples (from 15 minutes to 10 minutes) to align with the assay validation parameters for the measurement of lipoprotein lipase (LPL) activity; made an addition to the platelet monitoring rule to allow for more frequent monitoring when appropriate; provided guidance to investigators with enrolled FCS subjects who also had T2DM; provided specific glucose monitoring rules for subjects on insulin and oral antidiabetic medications. The definition of documented severe hypoglycemia was included and safety monitoring rules were defined. Also, specific monitoring rules were incorporated into the protocol for hyperglycaemic events; modified the statistical analysis section to preserve the integrity of the randomisation and to clarify the statistical analyses methods in accordance with regulatory agency requests.
01 December 2015	Updated the approximate anticipated number of subjects that could enrol into the study (approximately 70 subjects).
19 April 2016	Modified the clinical experience safety language to reflect updated blinded safety data from ongoing studies; indicated that the 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 the pregnancy testing; added haematology blood draws at Weeks 12, 16, 22, 25, 29, 35, 41, 47, and 51 to more frequently assess platelet counts; allowed blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, 29, 32, 35, 41, 44, 47, 51, and 58 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 should 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; added language to the safety monitoring for insulin, oral antidiabetic medication and glucose that all subjects, including those not on insulin, who used a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit; clarified guidance on determining relatedness of a suspected unexpected serious adverse reaction (SUSAR); added language to justify the increase in the number of subjects in the previous amendment (Amendment 3 dated 01 December 2015).
05 May 2016	Added language that any case of a platelet count ≤ 50,000/cubic millimetres (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 be rechecked and determined not to have met a stopping rule before dosing could continue; made minor changes to correct errors and/or to improve the overall clarity of the protocol.

06 June 2016	Added haematology blood draws so that platelet counts (PCs) were measured every 2 weeks (Ws) during treatment period and every 2 Ws for first 6 Ws after last dose (D) of study drug; updated platelet safety monitoring rules; added language that if there were no reportable PC within 14 days of last PC, investigator would contact subject to hold dosing until a new PC was obtained and reviewed; added language to indicate that all PC results would be promptly reviewed by investigator to ensure that count had not met stopping rule and to determine whether rate of decline was suggestive that subject could be approaching D pause rule of 75000/mm^3(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 300 mg every 2 Ws or a reduced D of 150 mg/ W and only if approved by sponsor medical monitor; added language to indicate that in event of any PC less than 25000/M, or a PC less than 50000/M that occurred while subject was on dosing at 300 mg every 2 Ws or 150 mg/W, then dosing of a subject with study drug (volanesorsen or placebo) would be stopped permanently. PC would be monitored daily until 2 successive values showed improvement then monitored every 2-3 days until PC was stable; added language to indicate that administration of steroids was recommended for subjects whose PC was less than 25000/M and to provide treatment guidelines for administration of steroids; added a table summarising actions to be taken in event of a low PC; added language to clarify definition of pharmacokinetic (PK) population; added language to evaluate effect of gender on 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 as limited wash-out data were expected; made minor changes to correct errors and/or to improve overall clarity of protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported