Clinical trial results:
An Open-Label Study of Volanesorsen Administered Subcutaneously to Subjects with Familial Chylomicronemia Syndrome (FCS)

Summary

EudraCT number	2015-003755-21
Trial protocol	GB NL ES DE FR IT
Global end of trial date	15 January 2020

Results information

Result version number	v1 (current)
This version publication date	19 August 2021
First version publication date	19 August 2021

Trial information

Trial identification

Sponsor protocol code	ISIS304801-CS7

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02658175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Akcea Therapeutics
Sponsor organisation address	22 Boston Wharf Road, 9th Floor, Boston, MA, 02210, United States,
Public contact	Vickie Alexander, Ionis Pharmaceuticals, Inc., +1 760 603-3858, valexander@ionisph.com
Scientific contact	Vickie Alexander, Ionis Pharmaceuticals, Inc., +1 760 603-3858, valexander@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	15 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 milligrams [mg]) in subjects with familial chylomicronemia syndrome (FCS).

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	23 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	68
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	62
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 19 study centers in Canada, France, Italy, Netherlands, South Africa, Spain, United Kingdom and the United States from 23 December 2015 to 15 January 2020.

Pre-assignment

Screening details:

A total of 68 subjects were enrolled into this study.

Period 1

Period 1 title	Treatment Period: Weeks 1 to 52
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment-naïve Group (Treatment Period)

Arm description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), were to receive 300 mg of volanesorsen as single subcutaneous (SC) injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Arm title	CS6-Volanesorsen (Treatment Period)

Arm description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Arm title	CS16-Volanesorsen (Treatment Period)

Arm description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Arm type	Experimental

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Number of subjects in period 1	Treatment-naïve Group (Treatment Period)	CS6-Volanesorsen (Treatment Period)	CS16-Volanesorsen (Treatment Period)
Started	51	14	3
Completed	36	7	3
Not completed	15	7	0
Adverse Event (AE) or Serious Adverse Event (SAE)	8	5	-
Voluntary Withdrawal	6	2	-
Investigator Judgment	1	-	-

Period 2

Period 2 title	1st Extended Treatment: Weeks 53 to 104
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment-naïve Group (1st Extended Treatment)

Arm description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Arm title	CS6-Volanesorsen (1st Extended Treatment)

Arm description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Arm title	CS16-Volanesorsen (1st Extended Treatment)

Arm description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Number of subjects in period 2	Treatment-naïve Group (1st Extended Treatment)	CS6-Volanesorsen (1st Extended Treatment)	CS16-Volanesorsen (1st Extended Treatment)
Started	36	7	3
Completed	15	5	1
Not completed	21	2	2
AE or SAE	7	-	-
Voluntary Withdrawal	4	-	1
Investigator Judgment	1	-	-
Unspecified	1	-	1
Transferred to Early Access Programs	8	2	-

Period 3

Period 3 title	2nd Extended Treatment: Weeks 105 to156
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment-naïve Group (2nd Extended Treatment)

Arm description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), following the Week 104 visit of this study, France subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Arm title	CS16-Volanesorsen (2nd Extended Treatment)

Arm description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, following the Week 104 visit of this study, France subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

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

Dosage and administration details:

Volanesorsen (ISIS 304801) 300 mg as a weekly SC injection.

Number of subjects in period 3[1]	Treatment-naïve Group (2nd Extended Treatment)	CS16-Volanesorsen (2nd Extended Treatment)
Started	1	1
Completed	0	0
Not completed	1	1
AE or SAE	-	1
Transferred to Commercial Treatment	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only those subjects in France who continued into the 2nd extended treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment-naïve Group (Treatment Period)

Reporting group description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), were to receive 300 mg of volanesorsen as single subcutaneous (SC) injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group title	CS6-Volanesorsen (Treatment Period)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group title	CS16-Volanesorsen (Treatment Period)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group values	Treatment-naïve Group (Treatment Period)	CS6-Volanesorsen (Treatment Period)	CS16-Volanesorsen (Treatment Period)
Number of subjects	51	14	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47	48	48
standard deviation	± 14	± 14	± 11
Gender categorical Units: Subjects			
Female	34	7	2
Male	17	7	1
Race Units: Subjects			
White	39	11	3
Asian	11	3	0
Other Race	1	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	49	14	3
Fasting Triglyceride (TG) Units: milligrams per decilitre (mg/dL)			
arithmetic mean	2341	1523	2081
standard deviation	± 1193	± 946	± 706

Reporting group values	Total		
Number of subjects	68		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	43		
Male	25		
Race Units: Subjects			
White	53		
Asian	14		
Other Race	1		
Ethnicity Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	66		
Fasting Triglyceride (TG) Units: milligrams per decilitre (mg/dL) arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Treatment-naïve Group (Treatment Period)

Reporting group description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), were to receive 300 mg of volanesorsen as single subcutaneous (SC) injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group title	CS6-Volanesorsen (Treatment Period)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group title	CS16-Volanesorsen (Treatment Period)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules.

Reporting group title	Treatment-naïve Group (1st Extended Treatment)

Reporting group description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

Reporting group title	CS6-Volanesorsen (1st Extended Treatment)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

Reporting group title	CS16-Volanesorsen (1st Extended Treatment)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, following the Week 52 visit of this study, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

Reporting group title	Treatment-naïve Group (2nd Extended Treatment)

Reporting group description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), following the Week 104 visit of this study, France subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

Reporting group title	CS16-Volanesorsen (2nd Extended Treatment)

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, following the Week 104 visit of this study, France subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105

to Week 156) of this study until an expanded access program was approved and available in their country. Subjects were allowed dose adjustment/dose reduction based on monitoring rule.

Subject analysis set title	Treatment-naïve Group
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52. Dose adjustment/dose reduction based on monitoring rules was allowed. Following Week 52, subjects could participate in an expanded access program or continue treatment with 300 mg of volanesorsen as single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) until an expanded access program was approved and available in their country. Subjects not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Subject analysis set title	CS6-Volanesorsen
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules. Following the Week 52 visit, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects who were not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Subject analysis set title	CS16-Volanesorsen
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules. Following the Week 52 visit, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects who were not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Primary: Mean Percent Change From Baseline in Fasting Triglyceride (TG)

End point title	Mean Percent Change From Baseline in Fasting Triglyceride (TG)[1]

End point description:

Baseline for treatment-naïve group was average of open-label Day 1 pre-dose assessment and last measurement prior to open-label Day 1. Baseline for CS6-volanesorsen and CS16-volanesorsen arm groups was average of index study Day 1 pre-dose assessment and the last measurement prior index study Day 1. The values at the Month 3 analysis time point were defined as the average of the Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. The Month 6 analysis time point was at the end of Month 6, and the values were defined as the average of the Week 25 (Day 169) and Week 26 (Day 176) fasting assessments. The values at the Month 12 analysis time point were defined as the average of the Week 50 (Day 344) and Week 52 (Day 358) fasting assessments. Full Analysis Set (FAS) included all subjects who were enrolled and received at least 1 dose of study drug and who had an open-label study baseline TG assessment. "number analyzed" ("n") signifies subjects evaluable for this OM at specified time

End point type	Primary

End point timeframe:

Baseline and Months 3, 6, and 12

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: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Treatment-naïve Group	CS6-Volanesorsen	CS16-Volanesorsen	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change at Month 3 (n=47, 14, 3)	-59.8 (± 37.0)	-49.2 (± 34.8)	-64.9 (± 9.1)	
Percent Change at Month 6 (n=49, 13, 3)	-45.5 (± 42.9)	-54.8 (± 23.8)	-43.0 (± 19.7)	
Percent Change at Month 12 (n=45, 12, 3)	-36.3 (± 44.2)	-35.1 (± 45.6)	-41.6 (± 36.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[2]

End point description:

An adverse event (AE) was defined as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered related to the investigational drug product. A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. Safety Set included all subjects who were enrolled and received at least one dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug to end of follow-up period [Up to Week 182]

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: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Treatment-naïve Group	CS6-Volanesorsen	CS16-Volanesorsen	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	51	14	3	
Units: count of subjects	51	14	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to end of follow-up period [Up to Week 182]

Adverse event reporting additional description:

Safety Set included all subjects who were enrolled and 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	Treatment-naïve Group

Reporting group description:

Treatment naïve group included combined group of ISIS 304801-CS7 (CS7-New) study subject and subject on placebo in index studies (ISIS 304801-CS6- Placebo [NCT02211209] and ISIS 304801-CS16-Placebo [NCT02300233]), were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52. Dose adjustment/dose reduction based on monitoring rules was allowed. Following Week 52, subjects could participate in an expanded access program or continue treatment with 300 mg of volanesorsen as single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) until an expanded access program was approved and available in their country. Subjects not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Reporting group title	CS6-Volanesorsen

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS6 (NCT02211209) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules. Following the Week 52 visit, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects who were not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Reporting group title	CS16-Volanesorsen

Reporting group description:

Subjects with FCS rolling over from the ISIS 304801-CS16 (NCT02300233) index study after receiving volanesorsen, were to receive 300 mg of volanesorsen as a single SC injection once weekly for Weeks 1-52 of this study. Subjects were allowed dose adjustment/dose reduction based on monitoring rules. Following the Week 52 visit, subjects had the option of participating in an expanded access program or continuing treatment with 300 mg of volanesorsen as a single SC injection once-weekly for up to an additional 52 weeks (Weeks 53-104) and in France subjects, up to an additional 104 weeks for total of 156 weeks of treatment (Weeks 105 to Week 156) of this study until an expanded access program was approved and available in their country. Subjects who were not participating in an expanded access program were to enter a 13-week post-treatment evaluation period and in France, subjects not continuing treatment were to enter a 26-week post-treatment follow-up period.

Serious adverse events	Treatment-naïve Group	CS6-Volanesorsen	CS16-Volanesorsen
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 51 (25.49%)	2 / 14 (14.29%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	2 / 51 (3.92%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Renal and urinary disorders			
Focal segmental glomerulosclerosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Myalgia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (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
Tendon calcification			

subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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			
Diverticulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Urinary tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	0 / 3 (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	Treatment-naïve Group	CS6-Volanesorsen	CS16-Volanesorsen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 51 (100.00%)	14 / 14 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 51 (7.84%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Flushing			

subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	36 / 51 (70.59%)	7 / 14 (50.00%)	1 / 3 (33.33%)
occurrences (all)	455	64	2
Injection site pain			
subjects affected / exposed	21 / 51 (41.18%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	255	46	0
Injection site swelling			
subjects affected / exposed	14 / 51 (27.45%)	5 / 14 (35.71%)	0 / 3 (0.00%)
occurrences (all)	226	32	0
Injection site pruritus			
subjects affected / exposed	11 / 51 (21.57%)	4 / 14 (28.57%)	0 / 3 (0.00%)
occurrences (all)	167	59	0
Injection site discolouration			
subjects affected / exposed	12 / 51 (23.53%)	1 / 14 (7.14%)	1 / 3 (33.33%)
occurrences (all)	218	4	1
Injection site induration			
subjects affected / exposed	11 / 51 (21.57%)	2 / 14 (14.29%)	1 / 3 (33.33%)
occurrences (all)	31	3	1
Pyrexia			
subjects affected / exposed	11 / 51 (21.57%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	25	20	0
Fatigue			
subjects affected / exposed	7 / 51 (13.73%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	12	10	0
Chills			

subjects affected / exposed	6 / 51 (11.76%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	9	30	0
Asthenia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 14 (14.29%)	2 / 3 (66.67%)
occurrences (all)	4	2	12
Injection site bruising			
subjects affected / exposed	5 / 51 (9.80%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Injection site haematoma			
subjects affected / exposed	5 / 51 (9.80%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Injection site oedema			
subjects affected / exposed	5 / 51 (9.80%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	6	1	0
Injection site haemorrhage			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	3	4	0
Pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	4	6	0
Injection site hypoaesthesia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Injection site reaction			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Injection site urticaria			
subjects affected / exposed	1 / 51 (1.96%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	34	0
Peripheral swelling			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Injection site dryness			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Cyst			

subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Feeling hot			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Influenza like illness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection site mass			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	7	0
Local swelling			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	2 / 51 (3.92%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Ovarian cyst			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Testicular cyst			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 51 (17.65%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	12	5	0
Epistaxis			

subjects affected / exposed	3 / 51 (5.88%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Nasal congestion			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Rhinorrhoea			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Bronchitis chronic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	9 / 51 (17.65%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	15	2	0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 51 (3.92%)	0 / 14 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	2
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Insomnia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Investigations			

Platelet count decreased			
subjects affected / exposed	15 / 51 (29.41%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	39	11	0
Haemoglobin decreased			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	6	1	0
Haematocrit decreased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Cold agglutinins			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Fibrin D dimer increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 51 (7.84%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Ligament rupture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 51 (23.53%)	4 / 14 (28.57%)	0 / 3 (0.00%)
occurrences (all)	19	16	0
Dizziness			
subjects affected / exposed	5 / 51 (9.80%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	5	3	0
Paraesthesia			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Hypoaesthesia			

subjects affected / exposed	3 / 51 (5.88%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Sciatica			
subjects affected / exposed	2 / 51 (3.92%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Polyneuropathy			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	9 / 51 (17.65%)	1 / 14 (7.14%)	2 / 3 (66.67%)
occurrences (all)	10	1	3
Anaemia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Lymphopenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Microcytic anaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	4	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 51 (27.45%)	5 / 14 (35.71%)	3 / 3 (100.00%)
occurrences (all)	23	10	7
Nausea			
subjects affected / exposed	11 / 51 (21.57%)	4 / 14 (28.57%)	1 / 3 (33.33%)
occurrences (all)	25	16	1
Vomiting			

subjects affected / exposed	9 / 51 (17.65%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	14	5	0
Diarrhoea			
subjects affected / exposed	6 / 51 (11.76%)	2 / 14 (14.29%)	1 / 3 (33.33%)
occurrences (all)	10	2	4
Abdominal pain upper			
subjects affected / exposed	7 / 51 (13.73%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	7	0	0
Dyspepsia			
subjects affected / exposed	4 / 51 (7.84%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	4	6	0
Abdominal distension			
subjects affected / exposed	5 / 51 (9.80%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	32	0	0
Abdominal discomfort			
subjects affected / exposed	4 / 51 (7.84%)	0 / 14 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Constipation			
subjects affected / exposed	2 / 51 (3.92%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Abdominal tenderness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Anal haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Diverticulum			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pancreatitis chronic			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Periodontal disease			

subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	4 / 51 (7.84%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Pruritus			
subjects affected / exposed	1 / 51 (1.96%)	2 / 14 (14.29%)	2 / 3 (66.67%)
occurrences (all)	2	2	19
Rash			
subjects affected / exposed	3 / 51 (5.88%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	4	3	0
Alopecia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Erythema			
subjects affected / exposed	2 / 51 (3.92%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Night sweats			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Rash vesicular			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Skin hypertrophy			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Proteinuria			

subjects affected / exposed	4 / 51 (7.84%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	6	2	0
Albuminuria			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Renal cyst			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 14 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Hyperthyroidism			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 51 (19.61%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	18	25	0
Pain in extremity			
subjects affected / exposed	7 / 51 (13.73%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	8	49	0
Back pain			
subjects affected / exposed	7 / 51 (13.73%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	12	2	0
Myalgia			
subjects affected / exposed	5 / 51 (9.80%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	9	2	0
Musculoskeletal pain			
subjects affected / exposed	3 / 51 (5.88%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	6	8	0
Pain in jaw			
subjects affected / exposed	2 / 51 (3.92%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	2	7	0
Intervertebral disc protrusion			

subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Joint swelling			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Neck pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	3	6	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Plantar fasciitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Seronegative arthritis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 51 (41.18%)	4 / 14 (28.57%)	0 / 3 (0.00%)
occurrences (all)	33	8	0
Influenza			
subjects affected / exposed	8 / 51 (15.69%)	5 / 14 (35.71%)	0 / 3 (0.00%)
occurrences (all)	9	5	0
Urinary tract infection			
subjects affected / exposed	8 / 51 (15.69%)	3 / 14 (21.43%)	0 / 3 (0.00%)
occurrences (all)	15	5	0
Bronchitis			
subjects affected / exposed	5 / 51 (9.80%)	2 / 14 (14.29%)	1 / 3 (33.33%)
occurrences (all)	7	2	1
Gastroenteritis			
subjects affected / exposed	5 / 51 (9.80%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Ear infection			
subjects affected / exposed	4 / 51 (7.84%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	4	1	0

Sinusitis			
subjects affected / exposed	4 / 51 (7.84%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	7	1	0
Atypical pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 51 (1.96%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	5	0
Vitamin D deficiency			
subjects affected / exposed	0 / 51 (0.00%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	Updated the approximate anticipated number of subjects that may enroll into the study (approximately 70 subjects) so that the number of subjects is reflective of the estimated number of qualified subjects from the ISIS 304801-CS6 and ISIS 304801- CS16 Index Studies. • Defined the specific subject population from ISIS 304801-CS16 who will be allowed to enter the Open-label Extension Study. • Clarification of when final assessments from the ISIS 304801- CS6 and ISIS 304801-CS16 Index Studies may be used for enrollment into ISIS 304801-CS7. • Clarification of how food and alcohol were monitored during the study. • An addition to the platelet monitoring rule language to allow for more frequent monitoring was included. • Guidance to Investigators with enrolled FCS subjects who also had Type 2 diabetes mellitus. Specific glucose monitoring rules were provided 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 hyperglycemic events.
22 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 is only acceptable as true abstinence, i.e., when it was in line with the preferred and usual lifestyle of the subject. • Added lipoprotein lipase activity as a qualification assessment for ISIS 304801-CS16 rollover subjects. • Added genetic testing as a qualification assessment for ISIS 304801-CS16 rollover subjects. • Increased the frequency of the pregnancy testing. • Added hematology 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. Allowed blood sampling at the 24-hour PK blood draw to be conducted by a home healthcare nurse. • Added language that each time a hematology lab was drawn and sent to the central laboratory for analysis, an additional sample should be collected in parallel and analyzed locally, to reduce the occurrence of unreportable hematology results. • Provided guidance that the length of fasting should preferably not be more than 12 hours. • Updated the 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 use 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 event (SUSAR).
09 May 2016	Added language that any case of a platelet count less than or equal to (≤) 50,000/ cubic millimeter (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 treatment could continue.

06 June 2016	Added hematology blood draws for platelet counts to be measured every 2 weeks during the treatment period and every 2 weeks for the first 6 weeks after the last dose of study drug. • Updated the platelet safety monitoring rules. • If there was no reportable platelet count within 14 days of the last platelet count, subject would hold treatment until a new platelet count is obtained and reviewed. • Added language to indicate that all platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the subject could be approaching the dose pause rule of 75,000/mm^3. • Changed the platelet dose pause/stopping rule from 50,000/mm^3 to 75,000/mm^3 and that when platelet count returns to greater than or equal to (≥) 100,000/mm^3 treatment may be continued but at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week and only if approved by the Sponsor Medical Monitor. • Added language to indicate that in the event of any platelet count less than 25,000/mm^3, or a platelet count less than 50,000/mm^3 that occured while the subject was on treatment at 300 mg every 2 weeks or 150 mg per week, then treatment of a subject with volanesorsen would be stopped permanently. Platelet count would be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable. • Added language to indicate that administration of steroids was recommended for subjects whose platelet count was less than 25,000/mm^3 and to provide treatment guidelines for the administration of steroids. • Added a table summarizing actions to be taken in the event of a low platelet count. • Added language to indicate that subjects would receive a suitable dose or dose frequency of volanesorsen, when they enter this CS7 study, based on safety/tolerability or non safety/tolerability dosing rules.
06 July 2016	Provisions to enroll FCS subjects in the open label study who did not participate in the ISIS 304801–CS6 or ISIS 304801–CS16 Index Studies. • Clarified the protocol which then specified 3 subject groups, with assignment based on prior involvement in Index Studies of ISIS 304801: - Group 1: ISIS 304801-CS6 (Index Study) rollover FCS subjects - Group 2: ISIS 304801-CS16 (Index Study) rollover FCS subjects - Group 3: FCS subjects who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 Index Studies •Removed language that indicated that lipoprotein lipase (LPL) activity can be measured if needed for study qualification for subjects in Groups 2 and 3. • Added language to indicate that a second study drug rechallenge would not be allowed following a platelet count decrease below 75,000/mm^3. • Provided clarifications to the platelet safety monitoring rules. • Added language to indicate that subjects who discontinue early from study drug, or the study, should be followed as per the platelet monitoring rules for the first 6 weeks after discontinuing study drug and the next platelet count should be taken within at least 6 weeks so that subjects would be monitored for at least 12 weeks after discontinuing study drug.
18 November 2016	Provision to allow subjects who complete the 52-week treatment period to participate in an expanded access program or continue treatment for up to an additional 52 weeks until an expanded access program was approved and available in their country. Subjects not participating in an expanded access program would enter the 13- week post treatment evaluation period. • The following assessments were added: Troponin I; labs to be performed in the event of a platelet count < 75,000/mm^3; platelet bound autoantibody testing at Baseline (may be done); plus medical history, hepatitis B, C, and human immunodeficiency virus (HIV) at Screening (Group 3 subjects).
07 April 2017	Updated the platelet safety monitoring rules. • Added LPL activity of ≤ 20 percent (%) of normal in medical history as an inclusion criteria for Group 2 and 3 subjects as had been allowed for Group 1 subjects. • Added platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3) for Group 3 subjects. •Assessment of acute pancreatitis in medical history in Group 2 subjects. • Added archive blood sample for potential gene sequencing related to High Throughput Genomic (HTG) (Group 3; Group 2 if not available from Index Study). • Blood viscosity (may be done) to assess potential benefit of study drug administration, and platelet aggregation (may be done) to assess platelet function.

25 May 2018	Prolonged the extended treatment period an additional 52 weeks.
21 November 2018	Added the option for subjects to receive a study drug dose reduction as either 300 mg every two weeks (prefilled syringe) or 150 mg once-weekly (vial presentation), Clarified that discontinuation from the treatment period will be required for any subjects who are on a dose pause for ≥ 3 months, and removed the references to landmark visits (if subject stops drug treatment then they enter the follow-up period).
01 May 2019	Added an up to 52 weeks of additional treatment to the extended treatment period. • Clarified the option for subjects to receive a volanesorsen dose reduction of 300 mg every two weeks. • Clarified discontinuation of subjects from the treatment period who were on a dose pause for ≥ 3 months. • Removed the references to landmark visits (if subject stops treatment then they enter the follow-up period).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported