Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, with an Open Label Extension, Phase 2/3 Study of ISIS 304801 Administered Subcutaneously to Subjects with Familial Partial Lipodystrophy

Summary

EudraCT number	2015-000493-35
Trial protocol	DE BE PT ES NL GR IT
Global end of trial date	13 November 2019

Results information

Result version number	v2 (current)
This version publication date	07 November 2021
First version publication date	19 August 2021
Version creation reason	• Correction of full data set Sections such as subject disposition, baseline characteristics and endpoints were updated.

Trial information

Trial identification

Sponsor protocol code	ISIS-304801-CS17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02527343
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Ct., Carlsbad, CA, United States, 92010
Public contact	Joseph Tami, Ionis Pharmaceuticals, Inc., +1 760603-2430, jtami@ionisph.com
Scientific contact	Joseph Tami, Ionis Pharmaceuticals, Inc., +1 760603-2430, jtami@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	13 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of volanesorsen for reduction in severity of metabolic derangement in subjects with familial partial lipodystrophy (FPL) with hypertriglyceridemia and uncontrolled diabetes.

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	28 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	Brazil: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	40
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 12 study centers in the United States, Russia, Brazil, Germany, Belgium, Canada, and Netherlands from 28 December 2015 to 13 November 2019.

Pre-assignment

Screening details:

A total of 40 subjects were randomized into this study.

Period 1

Period 1 title	RT Period: Weeks 1 to 52
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Randomized Treatment Period: Placebo

Arm description:

Subjects received volanesorsen-matching placebo as a subcutaneous (SC) injection once-weekly from Weeks 1 to 52 of the randomized treatment (RT) period. Subjects were allowed dose adjustment based on monitoring rules.

Arm type	Placebo
Investigational medicinal product name	Volanesorsen-matching 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 as a SC injection.

Arm title	Randomized Treatment Period: Volanesorsen

Arm description:

Subjects received 300 mg of volanesorsen as a SC injection once-weekly from Weeks 1 to 52 of the randomized treatment period. Subjects were allowed dose adjustment based on monitoring rules.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Number of subjects in period 1	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen
Started	19	21
Completed	13	14
Not completed	6	7
Investigator's Judgement	1	-
Unspecified	4	3
Adverse Event (AE) or Serious-Adverse Event (SAE)	-	4
Voluntary withdrawal	1	-

Period 2

Period 2 title	RT Post Treatment Follow-up: Weeks 54-65
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Assessor, Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	No
Arm title	Randomized Post-Treatment Follow-up Period: Placebo

Arm description:

Following the randomized treatment period, subjects who received volanesorsen-matching placebo in randomized treatment period and did not enter the open label extension (OLE) period went straight to the 13-week post-treatment (PT) follow-up period.

Arm type	Placebo
Investigational medicinal product name	Volanesorsen-matching 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 as a SC injection.

Arm title	Randomized Post-Treatment Follow-up Period: Volanesorsen

Arm description:

Following the randomized treatment period, subjects who received 300 mg of volanesorsen in randomized treatment period and did not enter in the OLE period went straight to the 13-week post-treatment follow-up period.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Number of subjects in period 2	Randomized Post-Treatment Follow-up Period: Placebo	Randomized Post-Treatment Follow-up Period: Volanesorsen
Started	7	9
Completed	6	7
Not completed	1	2
AE or SAE	1	-
Unspecified	-	2

Period 3

Period 3 title	OLE Period-Year 1: Week 53 to 104
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Open-Label Extension Period: Placebo/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period, were to receive 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Arm title	Open-Label Extension Period: Volanesorsen/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period, received 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Number of subjects in period 3	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen
Started	12	12
Completed	1	3
Not completed	11	9
AE or SAE	2	1
Investigator's Judgement	1	-
Unspecified	5	7
Voluntary withdrawal	3	1

Period 4

Period 4 title	OLE Period-Year 2: Week 105 to 156
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Open-Label Extension Period: Placebo/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period, after Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection once-weekly for up to an additional 52 weeks (from Week 105 to 156). Subjects were allowed dose adjustment based on monitoring rules.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Arm title	Open-Label Extension Period: Volanesorsen/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized

treatment period, after Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection once-weekly for up to an additional 52 weeks (from Week 105 to 156). Subjects were allowed dose adjustment based on monitoring rules.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Number of subjects in period 4	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen
Started	1	2
Completed	0	0
Not completed	1	2
Unspecified	1	2

Period 5

Period 5 title	PT Follow-up: Weeks 104 to 169
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	OLE Post-Treatment Follow up Period: Placebo/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period and were not entered in the option for an additional 52 weeks of dosing in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects were allowed dose adjustment based on monitoring rules. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Arm title	OLE Post-Treatment Follow up Period: Volanesorsen/Volanesorsen

Arm description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period and were not entered in the option for an additional 52 weeks of dosing in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects were allowed dose adjustment based on monitoring rules. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

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

Dosage and administration details:

Volanesorsen 300 mg administered as a SC injection.

Number of subjects in period 5	OLE Post-Treatment Follow up Period: Placebo/Volanesorsen	OLE Post-Treatment Follow up Period: Volanesorsen/Volanesorsen
Started	12	12
Completed	11	11
Not completed	1	1
Unspecified	-	1
Voluntary withdrawal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Randomized Treatment Period: Placebo
Reporting group description:	
Subjects received volanesorsen-matching placebo as a subcutaneous (SC) injection once-weekly from Weeks 1 to 52 of the randomized treatment (RT) period. Subjects were allowed dose adjustment based on monitoring rules.	
Reporting group title	Randomized Treatment Period: Volanesorsen
Reporting group description:	
Subjects received 300 mg of volanesorsen as a SC injection once-weekly from Weeks 1 to 52 of the randomized treatment period. Subjects were allowed dose adjustment based on monitoring rules.	

Reporting group values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen	Total
Number of subjects	19	21	40
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48	46	
standard deviation	± 12	± 10	-
Gender categorical Units: Subjects			
Female	14	15	29
Male	5	6	11
Race Units: Subjects			
White	17	20	37
Asian	1	1	2
Other Race	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	18	20	38
Unknown or Not Reported	0	0	0
Fasting Triglycerides Units: milligrams per deciliter (mg/dL)			
arithmetic mean	1290.95	1241.31	
standard deviation	± 1296.19	± 1090.83	-
Hepatic Fat Fraction			
Number analyzed ("n") (n= 16, 17) signifies the number of subjects with data available for hepatic fat fraction.			
Units: percentage (Hepatic Fat Fraction)			
arithmetic mean	17.00	18.10	
standard deviation	± 7.52	± 8.41	-
Hemoglobin A1c Units: percentage of HbA1c			
arithmetic mean	8.25	7.84	

standard deviation	± 1.13	± 1.62	-
Short Form (SF)-36 Weighted Sum of Scores			
The SF-36 Health Survey is a 36-item, subject-reported survey of subject health. SF-36 consists of 8 health dimensions,which are weighted sums of the questions in each section. SF-36 included 36 questions related to 8 health dimensions:physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning,emotional role functioning, and mental health. Each dimension was scored on a scale of 0 to 100 where, higher score = better quality of life. "n" (n= 16, 17)= number of subjects with data available.			
Units: score on a scale			
arithmetic mean	48.51	46.31	
standard deviation	± 12.83	± 12.38	-
EQ-5D Questionnaires: Index Scores			
EQ-5D-5L: standardized health-related quality of life (QoL) questionnaire. EQ-5D-5L consists of 2 components: health state profile and VAS. EQ-5D health state profile comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. Number analyzed (n= 12, 17) = number of subjects with data available.			
Units: score on a scale			
arithmetic mean	0.83	0.84	
standard deviation	± 0.20	± 0.18	-
EQ-5D Questionnaires: Visual Analog Scale			
EQ-5D-5L is a standardized health-related QoL questionnaire EQ-5D-5L consists of two components: a health state profile and VAS. EQ-5D-5L- VAS is designed to rate the subject's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. Number analyzed (n= 12, 17) signifies the number of subjects with data available for EQ-5D Questionnaires: VAS.			
Units: score on a scale			
arithmetic mean	70	71	
standard deviation	± 18	± 18	-

End points

End points reporting groups

Reporting group title	Randomized Treatment Period: Placebo

Reporting group description:

Subjects received volanesorsen-matching placebo as a subcutaneous (SC) injection once-weekly from Weeks 1 to 52 of the randomized treatment (RT) period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Randomized Treatment Period: Volanesorsen

Reporting group description:

Subjects received 300 mg of volanesorsen as a SC injection once-weekly from Weeks 1 to 52 of the randomized treatment period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Randomized Post-Treatment Follow-up Period: Placebo

Reporting group description:

Following the randomized treatment period, subjects who received volanesorsen-matching placebo in randomized treatment period and did not enter the open label extension (OLE) period went straight to the 13-week post-treatment (PT) follow-up period.

Reporting group title	Randomized Post-Treatment Follow-up Period: Volanesorsen

Reporting group description:

Following the randomized treatment period, subjects who received 300 mg of volanesorsen in randomized treatment period and did not enter in the OLE period went straight to the 13-week post-treatment follow-up period.

Reporting group title	Open-Label Extension Period: Placebo/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period, were to receive 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Open-Label Extension Period: Volanesorsen/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period, received 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Open-Label Extension Period: Placebo/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period, after Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection once-weekly for up to an additional 52 weeks (from Week 105 to 156). Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Open-Label Extension Period: Volanesorsen/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period, after Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection once-weekly for up to an additional 52 weeks (from Week 105 to 156). Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	OLE Post-Treatment Follow up Period: Placebo/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period and were not entered in the option for an additional 52 weeks of dosing in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects were allowed dose adjustment based on monitoring rules. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

Reporting group title	OLE Post-Treatment Follow up Period: Volanesorsen/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period and were not entered in the option for an additional 52 weeks of dosing in the OLE

post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects were allowed dose adjustment based on monitoring rules. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

Primary: Randomized Treatment Period: Percent Change From Baseline to Month 3 in Fasting Triglycerides (TG)

End point title	Randomized Treatment Period: Percent Change From Baseline to Month 3 in Fasting Triglycerides (TG)

End point description:

Baseline was defined as the average of Day 1 predose fasting assessment and the last fasting measurement prior to Day 1 predose fasting assessment. Month 3 value was defined as the average of Week 12 and Week 13 fasting TG assessments of the randomized treatment period. The data was analyzed using an analysis of covariance (ANCOVA) model with the randomization stratification factor (diagnosis of disease with or without genetics and family history) and treatment group as factors and log-transformed baseline fasting TG as a covariate. Full analysis set (FAS) included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment. This endpoint is reported here for the randomized treatment period only, as per the planned analysis.

End point type	Primary

End point timeframe:

Baseline to Month 3

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percent change				
least squares mean (confidence interval 95%)	-21.64 (-60.85 to 17.57)	-88.47 (-133.56 to -43.38)		

Statistical analyses

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-66.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-104.17
upper limit	-29.48

Secondary: Randomized Treatment Period: Percent Change From Baseline in Hepatic Steatosis as Assessed by Hepatic Fat Fraction Using Magnetic Resonance Imaging (MRI)

End point title	Randomized Treatment Period: Percent Change From Baseline in Hepatic Steatosis as Assessed by Hepatic Fat Fraction Using Magnetic Resonance Imaging (MRI)

End point description:

Baseline was defined as the last non-missing assessment prior to the first dose of study drug in the randomized treatment period. Randomized treatment period: Month 6 value was defined as Week 25 or Week 26 for MRI assessment and Month 12 was defined as Week 50 or Week 52 for MRI assessment. Hepatic steatosis is a reversible condition in which large vacuoles of triglyceride fat accumulate in the liver cells, causing nonspecific inflammation. Hepatic Steatosis was assessed by hepatic fat fraction using MRI. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment.

End point type	Secondary

End point timeframe:

Baseline, Months 6 and 12

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percent change				
least squares mean (confidence interval 95%)				
Percent Change at Month 6	2.83 (-23.46 to 29.12)	-22.86 (-52.07 to 6.34)		
Percent Change at Month 12	1.46 (-30.49 to 33.42)	-51.87 (-87.87 to -15.87)		

Statistical analyses

Statistical analysis title	RT Period: Placebo vs Volanesorsen

Statistical analysis description:

Month 6

Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0736
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-25.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.03
upper limit	2.65

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Statistical analysis description:	
Month 12	
Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-53.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.71
upper limit	-18.95

Secondary: Open-Label Extension Period: Percent Change From Baseline in Hepatic Steatosis as Assessed by Hepatic Fat Fraction Using MRI

End point title	Open-Label Extension Period: Percent Change From Baseline in Hepatic Steatosis as Assessed by Hepatic Fat Fraction Using MRI

End point description:

Baseline was defined as the last non-missing assessment prior to the first dose of study drug in the randomized treatment period. Open-label extension period: Month 6 value was defined as Week 77 or Week 78 for MRI assessment and Month 12 value was defined as Week 102 or Week 104 for MRI assessment . Hepatic steatosis is a reversible condition in which large vacuoles of triglyceride fat accumulate in the liver cells, causing nonspecific inflammation. Hepatic Steatosis was assessed by hepatic fat fraction using MRI. FAS included all subjects who were randomized and received at least one dose of study drug in the open-label extension period, and who had a baseline fasting TG assessment. Here, "number analysed" ("n") signifies subjects evaluable for this endpoint at specified time points and overall number of subjects ("N") analyzed signifies subjects who were evaluable for OLE Period.

End point type	Secondary

End point timeframe:

Baseline, Months 6 and 12

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change at Month 6 (n=6, 5)	-18.4 (± 54.7)	-60.2 (± 43.6)		
Percent Change at Month 12 (n=2, 2)	-93.5 (± 44.4)	-22.1 (± 47.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Change From Baseline in Hemoglobin A1c (HbA1c)

End point title	Randomized Treatment Period: Change From Baseline in Hemoglobin A1c (HbA1c)

End point description:

Baseline was defined as the last non-missing assessment prior to the first dose of study drug. Randomized treatment period: The Month 3 value was defined as Week 13, Month 6 value was defined as Week 26, Month 9 value was defined as Week 38 and Month 12 value was defined as Week 52. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment.

End point type	Secondary

End point timeframe:

Baseline, Months 3, 6, 9, and 12

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percentage of HbA1c				
least squares mean (confidence interval 95%)				
Change at Month 3	-0.51 (-1.22 to 0.20)	-0.21 (-1.00 to 0.58)		
Change at Month 6	0.06 (-1.02 to 1.15)	0.26 (-0.98 to 1.50)		
Change at Month 9	0.68 (-0.49 to 1.85)	0.48 (-0.84 to 1.80)		
Change at Month 12	0.48 (-0.49 to 1.45)	0.28 (-0.78 to 1.35)		

Statistical analyses

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Statistical analysis description: Month 3	
Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4108
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	1.03

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Statistical analysis description: Month 6	
Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7308
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	1.34

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Statistical analysis description: Month 9	

Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7511
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	1.06

Statistical analysis title	RT Period: Placebo vs Volanesorsen
Statistical analysis description:	
Month 12	
Comparison groups	Randomized Treatment Period: Placebo v Randomized Treatment Period: Volanesorsen
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7659
Method	ANCOVA
Parameter estimate	Difference in Least Square Mean
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.52
upper limit	1.13

Secondary: Open Label Extension Period: Change From Baseline in HbA1c

End point title	Open Label Extension Period: Change From Baseline in HbA1c

End point description:

Baseline was defined as the last non-missing assessment prior to the first dose of study drug. Open-label extension period: Month 3 value was defined as Week 65, Month 6 value was defined as Week 78, Month 9 value was defined as Week 90 and Month 12 value was defined as Week 104. FAS included all subjects who were randomized and received at least one dose of study drug in the open-label extension period, and who had a baseline fasting TG assessment. Here, "n" signifies subjects evaluable for this endpoint at specified time points "N" analyzed signifies subjects who were evaluable for OLE Period.

End point type	Secondary

End point timeframe:

Baseline, Months 3, 6, 9, and 12

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Baseline, Months 3, 6, 9, and 12				
arithmetic mean (standard deviation)				
Change at Month 3 (n= 6, 8)	0.42 (± 1.54)	0.91 (± 2.18)		
Change at Month 6 (n= 6, 3)	0.35 (± 1.54)	-0.75 (± 0.35)		
Change at Month 9 (n= 2, 2)	0.35 (± 1.06)	-0.05 (± 0.64)		
Change at Month 12 (n= 2, 2)	0.00 (± 0.71)	0.30 (± 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Percentage of Participants Who Achieved Greater Than or Equal to (≥) 40% Reduction in Fasting Triglyceride and ≥ 30% Reduction of Hepatic Fat Fraction at Month 6

End point title	Randomized Treatment Period: Percentage of Participants Who Achieved Greater Than or Equal to (≥) 40% Reduction in Fasting Triglyceride and ≥ 30% Reduction of Hepatic Fat Fraction at Month 6

End point description:

The baseline of TG is defined as the average of Day 1 pre-dose fasting assessment and the last fasting measurement prior to Day 1 pre-dose fasting assessment. The baseline of hepatic fat fraction is defined as the last non-missing assessment prior to the first dose of study drug. Randomized treatment period: Month 6 value was defined as the average of Week 25 and Week 26 for fasting TG assessment and Week 25 or Week 26 for hepatic fat fraction. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment. This endpoint is reported here for the randomized treatment period only, as per the planned analysis.

End point type	Secondary

End point timeframe:

Month 6

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percentage of subjects				
number (not applicable)	5.3	42.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Change From Baseline in Disease Burden Score

End point title	Randomized Treatment Period: Change From Baseline in Disease Burden Score

End point description:

The Disease Burden Score is a questionnaire that allows subjects to self-report their chronic conditions and then assess the degree to which each condition interferes with daily activities.

End point type	Secondary

End point timeframe:

From the first dose of study drug to Week 52

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: score on scale				
number (not applicable)				

Notes:

[1] - Data for this endpoint was not collected due to the change in planned analysis.

[2] - Data for this endpoint was not collected due to the change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label Extension Period: Change From Baseline in Disease Burden Score

End point title	Open-Label Extension Period: Change From Baseline in Disease Burden Score

End point description:

The Disease Burden Score is a questionnaire that allows subjects to self-report their chronic conditions and then assess the degree to which each condition interferes with daily activities.

End point type	Secondary

End point timeframe:

From the first dose of study drug in open label extension period to Week 117

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: score on scale				
number (not applicable)				

Notes:

[3] - Data for this endpoint was not collected due to the change in planned analysis.

[4] - Data for this endpoint was not collected due to the change in planned analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Patient-Reported Pain

End point title	Randomized Treatment Period: Patient-Reported Pain

End point description:

Patient-reported pain was assessed by rating pain symptoms at its worst and least for the last 24 hours, on average, and at the moment, with 0 as the lowest score (no pain) and 10 as the highest score (worst pain as you can imagine). Patient-reported pain was also assessed by rating pain symptoms (rate pain on average, rate pain right now) that interfered with general activity, interfered with mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, with 0 as the lowest score (did not interfered) and 10 as the highest score (completely interfered). The scores from each assessment time point were averaged for all of the below reported categories. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment. Here, overall number of subjects analyzed ("N") signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to Week 52

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: score on a scale				
arithmetic mean (standard deviation)				
Rate Pain at its Worst Last 24 Hours	3.28 (± 2.79)	3.57 (± 2.72)		
Rate Pain at its Least Last 24 Hours	2.45 (± 2.46)	2.59 (± 2.43)		
Rate Pain on Average	3.08 (± 2.62)	3.16 (± 2.47)		
Rate Pain Right Now	2.72 (± 2.59)	2.96 (± 2.50)		
General Activity	2.43 (± 2.80)	2.83 (± 2.57)		
Interfere With Mood	2.31 (± 2.88)	2.98 (± 2.59)		
Walking Ability	2.35 (± 2.96)	2.79 (± 2.59)		
Normal Work	2.37 (± 2.84)	2.89 (± 2.56)		
Relations With Other People	2.23 (± 2.79)	2.62 (± 2.67)		
Sleep	2.75 (± 2.95)	2.73 (± 2.75)		
Enjoyment of Life	2.42 (± 2.82)	2.68 (± 2.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Open Label Extension Period: Patient-Reported Pain

End point title	Open Label Extension Period: Patient-Reported Pain

End point description:

Patient-reported pain was assessed by rating pain symptoms at its worst and least for the last 24 hours, on average, and at the moment, with 0 as the lowest score (no pain) and 10 as the highest score (worst pain as you can imagine). Patient-reported pain was also assessed by rating pain symptoms (rate pain on average, rate pain right now) that interfered with general activity, interfered with mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, with 0 as the lowest score (did not interfered) and 10 as the highest score (completely interfered). The scores from each assessment time point were averaged for all of the below reported categories. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the first dose of study drug in open label extension period up to Week 117

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: score on a scale				
arithmetic mean (standard deviation)				
Rate Pain at its Worst Last 24 Hours	1.70 (± 1.18)	3.82 (± 2.97)		
Rate Pain at its Least Last 24 Hours	0.95 (± 1.04)	2.78 (± 2.60)		
Rate Pain on Average	1.35 (± 1.22)	3.16 (± 2.72)		
Rate Pain Right Now	1.28 (± 1.18)	3.49 (± 2.99)		
General Activity	1.03 (± 1.45)	3.28 (± 2.90)		
Interfere With Mood	1.27 (± 1.46)	3.23 (± 2.94)		
Walking Ability	1.05 (± 1.50)	3.51 (± 2.83)		
Normal Work	1.08 (± 1.40)	3.48 (± 2.98)		
Relations With Other People	1.08 (± 1.48)	3.18 (± 3.09)		
Sleep	1.51 (± 1.83)	3.13 (± 3.35)		
Enjoyment of Life	1.23 (± 1.65)	3.33 (± 2.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Patient-Reported Hunger

End point title	Randomized Treatment Period: Patient-Reported Hunger

End point description:

Patient-reported hunger was assessed by subjects who completed a questionnaire about: how hungry you feel, how satisfied you feel, how full you feel, how much you think you can eat, like to eat something sweet, like to eat something salty, like to eat something savory and like to eat something

fatty. Subjects also rated the palatability of meals that included visual appeal, smell, taste, and aftertaste. Scores of 1–39 were categorized as mild, 40–69 as moderate, and 70–100 as severe. The scores from each assessment time point were averaged for all of the below reported categories. FAS included all subjects who were randomized and received at least one dose of study drug in the randomized treatment period, and who had a baseline fasting TG assessment. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the first dose of study drug up to Week 52

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: score on a scale				
arithmetic mean (standard deviation)				
How Hungry You Feel	29.4 (± 20.7)	29.6 (± 14.4)		
How Satisfied You Feel	56.8 (± 22.4)	57.5 (± 15.1)		
How Full You Feel	62.6 (± 20.5)	56.6 (± 18.4)		
How Much You Think You Can Eat	33.6 (± 22.1)	36.8 (± 15.4)		
Like to Eat Something Sweet	71.0 (± 20.8)	54.8 (± 27.1)		
Like to Eat Something Salty	66.9 (± 21.7)	69.0 (± 20.2)		
Like to Eat Something Savory	65.2 (± 21.4)	66.8 (± 21.9)		
Like to Eat Something Fatty	77.9 (± 18.4)	75.9 (± 22.2)		
Visual Appeal	28.6 (± 20.5)	34.5 (± 21.0)		
Smell	23.4 (± 16.2)	25.4 (± 15.5)		
Taste	25.5 (± 18.3)	29.1 (± 14.5)		
Aftertaste	58.9 (± 27.5)	51.0 (± 24.6)		
Palatability	31.3 (± 20.1)	32.2 (± 15.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Open Label Extension Period: Patient-Reported Hunger

End point title	Open Label Extension Period: Patient-Reported Hunger

End point description:

Patient-reported hunger was assessed by subjects who completed a questionnaire about: how hungry you feel, how satisfied you feel, how full you feel, how much you think you can eat, like to eat something sweet, like to eat something salty, like to eat something savory and like to eat something fatty. Subjects also rated the palatability of meals that included visual appeal, smell, taste, and aftertaste. Scores of 1–39 were categorized as mild, 40–69 as moderate, and 70–100 as severe. The scores from each assessment time point were averaged for all of the below reported categories. FAS included all subjects who were randomized and received at least one dose of study drug in the open-label extension period, and who had a baseline fasting TG assessment. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the first dose of study drug in open label extension period up to Week 117

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: score on a scale				
arithmetic mean (standard deviation)				
How Hungry You Feel	29.9 (± 23.3)	33.2 (± 23.2)		
How Satisfied You Feel	54.2 (± 23.3)	56.3 (± 20.2)		
How Full You Feel	59.7 (± 22.2)	52.9 (± 24.4)		
How Much You Think You Can Eat	34.0 (± 21.8)	34.9 (± 21.5)		
Like to Eat Something Sweet	73.7 (± 25.4)	57.9 (± 24.0)		
Like to Eat Something Salty	65.7 (± 28.1)	61.9 (± 22.1)		
Like to Eat Something Savory	65.4 (± 24.7)	62.7 (± 30.5)		
Like to Eat Something Fatty	80.7 (± 18.1)	68.0 (± 30.4)		
Visual Appeal	14.9 (± 16.1)	35.3 (± 25.9)		
Smell	13.1 (± 14.3)	29.6 (± 21.6)		
Taste	13.6 (± 15.1)	32.9 (± 25.0)		
Aftertaste	48.1 (± 38.6)	56.9 (± 29.3)		
Palatability	24.4 (± 23.4)	37.3 (± 20.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Change From Baseline (CFB) in Mean Short Form-36 (SF-36) Weighted Sum of Scores

End point title	Randomized Treatment Period: Change From Baseline (CFB) in Mean Short Form-36 (SF-36) Weighted Sum of Scores

End point description:

The SF-36 Health Survey is a 36-item, subject-reported survey of subject health. SF-36 consists of 8 health dimensions,which are weighted sums of the questions in each section. SF-36 included 36 questions related to 8 health dimensions:physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning,emotional role functioning, and mental health. Each dimension was scored on a scale of 0 to 100 where, higher score = better quality of life. A positive change from Baseline indicates improvement. FAS was used. "n"=subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 26 and 52

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: score on a scale				
arithmetic mean (standard deviation)				
Vitality: Change at Week 13 (n= 13, 14)	-1.14 (± 7.33)	-0.21 (± 5.64)		
Vitality: Change at Week 26 (n= 12, 15)	-0.25 (± 9.00)	-0.79 (± 6.87)		
Vitality: Change at Week 52 (n= 7, 9)	-0.85 (± 6.11)	-3.30 (± 8.20)		
Physical Functioning: Change at Week 13 (n=13, 14)	-0.29 (± 4.81)	-0.41 (± 3.91)		
Physical Functioning: Change at Week 26 (n=12, 15)	-0.64 (± 6.49)	0.51 (± 5.29)		
Physical Functioning: Change at Week 52 (n= 7, 9)	-3.55 (± 4.05)	-2.76 (± 5.25)		
Bodily Pain: Change at Week 13 (n= 13, 14)	-0.46 (± 7.97)	0.75 (± 6.26)		
Bodily Pain: Change at Week 26 (n= 12, 15)	-1.98 (± 12.24)	0.19 (± 4.27)		
Bodily Pain: Change at Week 52 (n= 7, 9)	-0.29 (± 6.35)	-2.55 (± 8.48)		
GH Perceptions: Change at Week 13 (n= 13, 14)	-0.55 (± 5.57)	-0.58 (± 4.04)		
GH Perceptions: Change at Week 26 (n= 12, 15)	-1.59 (± 5.00)	0.54 (± 7.25)		
GH Perceptions: Change at Week 52 (n= 7, 9)	-1.50 (± 6.74)	-1.48 (± 4.53)		
PR Functioning: Change at Week 13 (n= 13, 14)	-0.52 (± 5.44)	-0.64 (± 4.61)		
PR Functioning: Change at Week 26 (n= 12, 15)	-2.06 (± 10.81)	0.75 (± 4.70)		
PR Functioning: Change at Week 52 (n= 7, 9)	-0.32 (± 2.02)	-2.00 (± 7.05)		
ER Functioning: Change at Week 13 (n= 13, 14)	-1.88 (± 4.63)	0.75 (± 6.85)		
ER Functioning: Change at Week 26 (n= 12, 15)	-2.90 (± 6.44)	0.23 (± 7.50)		
ER Functioning: Change at Week 52 (n= 7, 9)	-1.00 (± 5.94)	-5.42 (± 5.80)		
SR Functioning: Change at Week 13 (n= 13, 14)	-3.86 (± 9.85)	1.07 (± 4.02)		
SR Functioning: Change at Week 26 (n= 12, 15)	-5.01 (± 9.07)	-0.67 (± 3.21)		
SR Functioning: Change at Week 52 (n= 7, 9)	2.87 (± 4.89)	-2.79 (± 7.14)		
Mental Health: Change at Week 13 (n= 13, 14)	0.00 (± 6.67)	-0.19 (± 7.91)		
Mental Health: Change at Week 26 (n= 12, 15)	-2.18 (± 7.71)	1.05 (± 6.76)		
Mental Health: Change at Week 52 (n= 7, 9)	-0.37 (± 6.66)	-1.75 (± 6.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label Period: Change From Baseline in Mean SF-36 Weighted Sum of Scores

End point title	Open-Label Period: Change From Baseline in Mean SF-36 Weighted Sum of Scores

End point description:

The SF-36 Health Survey is a 36-item, subject-reported survey of subject health. SF-36 consists of 8 health dimensions,which are weighted sums of the questions in each section. SF-36 included 36 questions related to 8 health dimensions:physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning,emotional role functioning, and mental health. Each dimension was scored on a scale of 0 to 100 where, higher score = better quality of life. A positive change from Baseline indicates improvement. FAS was used. "n"= subjects evaluable for this endpoint at specified time points "N"= signifies subjects who were evaluable for OLE Period. 99999= SD was not estimable as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Baseline, Weeks 65, 78 and 104

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Vitality: Change at Week 65 (n= 2, 7)	4.46 (± 6.30)	-0.42 (± 13.88)		
Vitality: Change at Week 78 (n= 2, 1)	-2.98 (± 12.61)	-2.97 (± 99999)		
Vitality: Change at Week 104 (n= 1, 1)	2.97 (± 99999)	-5.94 (± 99999)		
Physical Functioning: Change at Week 65 (n= 2, 7)	-4.79 (± 6.77)	-1.37 (± 5.81)		
Physical Functioning: Change at Week 78 (n= 2, 1)	-3.83 (± 5.41)	0.00 (± 99999)		
Physical Functioning: Change at Week 104 (n= 1, 1)	0.00 (± 99999)	-1.91 (± 0)		
Bodily Pain: Change at Week 65 (n= 2, 7)	-2.42 (± 3.42)	0.40 (± 7.13)		
Bodily Pain: Change at Week 78 (n= 2, 1)	-7.26 (± 19.39)	-11.29 (± 99999)		
Bodily Pain: Change at Week 104 (n= 1, 1)	6.45 (± 99999)	-10.49 (± 99999)		
GH Perceptions: Change at Week 65 (n= 2, 7)	2.38 (± 3.36)	-2.38 (± 4.42)		
GH Perceptions: Change at Week 78 (n= 2, 1)	-2.86 (± 7.40)	-4.75 (± 99999)		
GH Perceptions: Change at Week 104 (n= 1, 1)	0 (± 99999)	-4.75 (± 99999)		
PR Functioning: Change at Week 65 (n= 2, 7)	0.00 (± 0.00)	-0.00 (± 6.22)		
PR Functioning: Change at Week 78 (n= 2, 1)	-10.11 (± 14.29)	-2.25 (± 99999)		

PR Functioning: Change at Week 104 (n= 1, 1)	0.00 (± 99999)	-4.50 (± 99999)		
ER Functioning: Change at Week 65 (n= 2, 7)	-1.74 (± 2.46)	-3.48 (± 11.37)		
ER Functioning: Change at Week 78 (n= 2, 1)	1.74 (± 2.46)	-10.45 (± 99999)		
ER Functioning: Change at Week 104 (n=1, 1)	3.48 (± 99999)	-10.45 (± 99999)		
SR Functioning: Change at Week 65 (n= 2, 7)	5.02 (± 7.09)	-2.15 (± 7.58)		
SR Functioning: Change at Week 78 (n= 2, 1)	-5.01 (± 7.09)	0.00 (± 99999)		
SR Functioning: Change at Week 104 (n= 1, 1)	0.00 (± 99999)	0.00 (± 99999)		
Mental Health: Change at Week 65 (n= 2, 7)	-5.23 (± 11.10)	-1.12 (± 13.67)		
Mental Health: Change at Week 78 (n= 2, 1)	6.54 (± 9.25)	-15.70 (± 99999)		
Mental Health: Change at Week 104 (n= 1, 1)	2.62 (± 99999)	0.00 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: Change From Baseline in Mean EQ-5D: Index Scores and Visual Analog Scale (VAS)

End point title	Randomized Treatment Period: Change From Baseline in Mean EQ-5D: Index Scores and Visual Analog Scale (VAS)

End point description:

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D-5L consists of two components: a health state profile and VAS. EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L- VAS is designed to rate the subject's current health state on a scale from 0 to 100, where 0 represents the worst imaginable health state and 100 represents the best imaginable health state. Negative CFB=worsening. Positive CFB=improvement. FAS was used. "n"=subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 26 and 52

End point values	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: score on a scale				
arithmetic mean (standard deviation)				
Index Score: Change at Week 13 (n= 8, 14)	0.05 (± 0.10)	-0.02 (± 0.06)		

Index Score: Change at Week 26 (n= 9, 15)	-0.11 (± 0.19)	-0.02 (± 0.12)		
Index Score: Change at Week 52 (n= 4, 9)	-0.08 (± 0.10)	-0.05 (± 0.07)		
EQ VAS Score: Change at Week 13 (n= 8, 14)	-2 (± 13)	-2 (± 15)		
EQ VAS Score: Change at Week 26 (n= 9, 15)	-11 (± 17)	-2 (± 14)		
EQ VAS Score: Change at Week 52 (n= 4, 9)	-13 (± 18)	-4 (± 16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label Period: Change From Baseline in Mean EQ-5D: Index and Visual Analog Scale (VAS) Scores

End point title	Open-Label Period: Change From Baseline in Mean EQ-5D: Index and Visual Analog Scale (VAS) Scores

End point description:

EQ-5D-5L: standardized health-related QoL questionnaire to provide simple, generic measure of health for clinical and economic appraisal. EQ-5D-5L consists of 2 components: health state profile and VAS. EQ-5D health state profile comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. 5D-5L systems are converted into a single index utility score between 0 to 1, higher score=better health state. EQ-5D-5L-VAS is designed to rate subject's current health state on a scale (0 to 100), where 0=worst imaginable health state and 100 =best imaginable health state. Negative CFB=worsening. Positive CFB=improvement. FAS was used. n=subjects evaluable at specified time points. N= subjects who were evaluable for OLE Period. 99999= SD was not estimable as only 1 subject was evaluable. 99999=Mean(SD) not evaluable where n=0.

End point type	Secondary

End point timeframe:

Baseline, Weeks 65, 78 and 104

End point values	Open-Label Extension Period: Placebo/Volanesorsen	Open-Label Extension Period: Volanesorsen/Volanesorsen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: score on a scale				
arithmetic mean (standard deviation)				
Index Score: Change at Week 65 (n= 0, 7)	99999 (± 99999)	-0.06 (± 0.08)		
Index Score: Change at Week 78 (n= 2, 1)	-0.02 (± 0.03)	-0.07 (± 99999)		
Index Score: Change at Week 104 (n= 1, 1)	0.00 (± 99999)	-0.27 (± 99999)		
EQ VAS Score: Change at Week 65 (n= 0, 7)	99999 (± 99999)	-4 (± 16)		
EQ VAS Score: Change at Week 78 (n= 2, 1)	-15 (± 22)	-6 (± 99999)		

EQ VAS Score: Change at Week 104 (n= 1, 1)	2 (± 99999)	0 (± 99999)		

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 169]

Adverse event reporting additional description:

Safety Population Set 1 included all subjects who were randomized and received at least one dose of study drug (volanesorsen or placebo) in the randomized treatment period. Safety Population Set 2 included all subjects who entered the OLE Period and received at least one dose of study drug (volanesorsen) in the OLE period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Randomized Treatment Period: Placebo

Reporting group description:

Subjects received volanesorsen-matching placebo as a SC injection once-weekly from Weeks 1 to 52 of the randomized treatment period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Randomized Treatment Period: Volanesorsen

Reporting group description:

Subjects received 300 mg of volanesorsen as a SC injection once-weekly from Weeks 1 to 52 of the randomized treatment period. Subjects were allowed dose adjustment based on monitoring rules.

Reporting group title	Randomized Post-Treatment Follow-up: Placebo

Reporting group description:

Following the randomized treatment period, subjects who received volanesorsen-matching placebo in randomized treatment period and did not enter the OLE period went straight to the 13-week post-treatment follow-up period.

Reporting group title	Randomized Post-Treatment Follow-up: Volanesorsen

Reporting group description:

Following the randomized treatment period, subjects who received 300 mg of volanesorsen in randomized treatment period and did not enter in the OLE period went straight to the 13-week post-treatment follow-up period.

Reporting group title	OLE and OLE Post-Treatment Follow-up: Placebo/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Placebo arm group who completed the randomized treatment period, received 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules. After Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection for up to an additional 52 weeks (from Week 105 to 156). Subjects who were not entered in the option for an additional 52 weeks of dosing in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

Reporting group title	OLE and OLE PT Follow-up: Volanesorsen/Volanesorsen

Reporting group description:

Subjects in the Randomized Treatment Period: Volanesorsen arm group who completed the randomized treatment period, received 300 mg of volanesorsen as a SC injection once-weekly for 52 weeks (from Weeks 53 to 104) in the OLE period. Subjects were allowed dose adjustment based on monitoring rules. After Week 104 of the OLE period, subjects had the option of continuing treatment with 300 mg of volanesorsen as a SC injection for up to an additional 52 weeks (from Week 105 to 156). Subjects who were not entered in the option for an additional 52 weeks of dosing in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of the first 52 weeks (from Weeks 53 to 104) of the OLE. Subjects who were entered in the OLE post-treatment period went straight to a 13-week post-treatment follow-up period after completion of Week 156 of the OLE.

Serious adverse events	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen	Randomized Post-Treatment Follow-up: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)	6 / 21 (28.57%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Partial seizures			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site inflammation			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Pancreatitis acute			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis necrotising			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (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
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 7 (14.29%)
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			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 7 (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
Dehydration			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Randomized Post-Treatment Follow-up: Volanesorsen	OLE and OLE Post-Treatment Follow-up: Placebo/Volanesorsen	OLE and OLE PT Follow-up: Volanesorsen/Volanesorsen
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	4 / 12 (33.33%)	4 / 12 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (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
Nervous system disorders			
Partial seizures			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
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	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site inflammation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (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
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (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
Pancreatitis necrotising			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Randomized Treatment Period: Placebo	Randomized Treatment Period: Volanesorsen	Randomized Post-Treatment Follow-up: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	21 / 21 (100.00%)	4 / 7 (57.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Squamous cell carcinoma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Asthma prophylaxis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sinus operation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	2 / 19 (10.53%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	2	3	0
Chills			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 19 (15.79%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	4	2	0
Influenza like illness			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Injection site bruising			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Injection site discolouration			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Injection site discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 19 (0.00%)	13 / 21 (61.90%)	0 / 7 (0.00%)
occurrences (all)	0	75	0
Injection site extravasation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site mass			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Injection site nodule			

subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	6	0
Injection site pain			
subjects affected / exposed	3 / 19 (15.79%)	7 / 21 (33.33%)	0 / 7 (0.00%)
occurrences (all)	3	53	0
Injection site paraesthesia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 19 (0.00%)	11 / 21 (52.38%)	0 / 7 (0.00%)
occurrences (all)	0	30	0
Injection site rash			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	8	0
Injection site reaction			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Injection site swelling			
subjects affected / exposed	0 / 19 (0.00%)	8 / 21 (38.10%)	0 / 7 (0.00%)
occurrences (all)	0	23	0
Injection site warmth			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypersensitivity			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vulval disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	1	7	0
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Pulmonary oedema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Depression			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sleep-related eating disorder			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Somnambulism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Albumin urine present			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Bacterial test			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Biopsy muscle			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood creatinine decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood fibrinogen increased			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood glucose fluctuation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood magnesium decreased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Blood phosphorus increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Echocardiogram abnormal			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glucose urine			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Glycosylated haemoglobin increased			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haematocrit decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
International normalised ratio increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 19 (0.00%)	5 / 21 (23.81%)	0 / 7 (0.00%)
occurrences (all)	0	8	0
Protein total increased			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Red blood cells urine			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rheumatoid factor increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Synovial fluid white blood cells positive			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urine protein, quantitative			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Arthropod sting			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chest injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Concussion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Exposure to toxic agent			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Postoperative wound complication			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Splinter			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Muscular dystrophy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Atrioventricular block complete			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Atrioventricular block second degree			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	3	1
Dysgeusia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysstasia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 19 (10.53%)	4 / 21 (19.05%)	0 / 7 (0.00%)
occurrences (all)	2	8	0
Neuropathy peripheral			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Syncope			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Lymphadenopathy			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Microcytosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Splenomegaly			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Eye swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ocular discomfort			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Visual impairment			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Abdominal pain			
subjects affected / exposed	3 / 19 (15.79%)	4 / 21 (19.05%)	0 / 7 (0.00%)
occurrences (all)	3	9	0
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Constipation			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	4 / 21 (19.05%)	0 / 7 (0.00%)
occurrences (all)	2	7	0
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Epulis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Food poisoning			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Gastric polyps			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Gastrointestinal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	4 / 21 (19.05%)	0 / 7 (0.00%)
occurrences (all)	4	10	0
Pancreatitis acute			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Subileus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	5	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Rash			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Skin exfoliation			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Xanthoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chromaturia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Micturition urgency			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Thyroid mass			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	1	6	0
Back pain			
subjects affected / exposed	2 / 19 (10.53%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	3	2	0
Bone pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscle fatigue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	2 / 19 (10.53%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	2	3	0
Muscular weakness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	5 / 19 (26.32%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	6	2	0
Plantar fasciitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Bacterial vaginosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Candida infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0

Fungal infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	6 / 21 (28.57%)	0 / 7 (0.00%)
occurrences (all)	2	7	0
Oral candidiasis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pulpitis dental			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	2	0

Sinusitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Skin infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Streptococcal infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tinea pedis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 19 (21.05%)	5 / 21 (23.81%)	0 / 7 (0.00%)
occurrences (all)	4	6	0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	5 / 21 (23.81%)	0 / 7 (0.00%)
occurrences (all)	0	8	0
Vaginal infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Appetite disorder			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	2 / 19 (10.53%)	4 / 21 (19.05%)	0 / 7 (0.00%)
occurrences (all)	2	4	0
Dyslipidaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	2 / 19 (10.53%)	2 / 21 (9.52%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Hyperuricaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	5 / 19 (26.32%)	3 / 21 (14.29%)	0 / 7 (0.00%)
occurrences (all)	7	8	0
Insulin resistance			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	0 / 7 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Randomized Post-Treatment Follow-up: Volanesorsen	OLE and OLE Post-Treatment Follow-up: Placebo/Volanesorsen	OLE and OLE PT Follow-up: Volanesorsen/Volanesorsen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)	11 / 12 (91.67%)	8 / 12 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Squamous cell carcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Asthma prophylaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Sinus operation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	7	0
Injection site discolouration			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

Injection site discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	0 / 9 (0.00%)	7 / 12 (58.33%)	1 / 12 (8.33%)
occurrences (all)	0	20	1
Injection site extravasation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Injection site induration			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	1 / 12 (8.33%)
occurrences (all)	0	37	4
Injection site mass			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injection site nodule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 9 (0.00%)	4 / 12 (33.33%)	1 / 12 (8.33%)
occurrences (all)	0	24	2
Injection site paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injection site pruritus			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Injection site rash			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Injection site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 9 (0.00%)	6 / 12 (50.00%)	2 / 12 (16.67%)
occurrences (all)	0	19	4

Injection site warmth			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Oedema peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	3	3
Peripheral swelling			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Vulval disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	2 / 12 (16.67%)
occurrences (all)	0	1	3
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pulmonary oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sleep-related eating disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Somnambulism			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Albumin urine present			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bacterial test			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Biopsy muscle			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatinine decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood fibrinogen increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood glucose fluctuation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Blood phosphorus increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood pressure increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Cardiac murmur			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Echocardiogram abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fibrin D dimer increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Glucose urine			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Haematocrit decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	3	10
Protein total increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Red blood cells urine			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rheumatoid factor increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Synovial fluid white blood cells positive			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Urine protein, quantitative			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Vitamin D decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Arthropod sting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Chest injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Exposure to toxic agent			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Meniscus injury			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Postoperative wound complication			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Splinter			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Muscular dystrophy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Atrioventricular block second degree			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysstasia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Neuropathy peripheral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Microcytosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Splenomegaly			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye swelling			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ocular discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	2 / 12 (16.67%)
occurrences (all)	0	1	3
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Epulis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Food poisoning			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastric polyps			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	3 / 12 (25.00%)	4 / 12 (33.33%)
occurrences (all)	0	10	7
Pancreatitis acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Subileus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	2 / 12 (16.67%)
occurrences (all)	0	8	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Xanthoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Chromaturia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Proteinuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Thyroid mass			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Muscle fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	7	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Plantar fasciitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bacterial vaginosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Candida infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Oral candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

Pulpitis dental			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Streptococcal infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Subcutaneous abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	6	2
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)	2 / 12 (16.67%)	1 / 12 (8.33%)
occurrences (all)	3	7	1
Vaginal infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Diabetes mellitus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	2 / 12 (16.67%)
occurrences (all)	0	14	2
Insulin resistance			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2016	To add hematology blood draws so that platelet counts were measured every 2 weeks during the treatment period and every 2 weeks for first 6 weeks after last dose of study drug. To allow blood sampling at additional study visit weeks to be conducted by a home healthcare service. To add language that any case of a platelet count ≤ 50,000/cubic millimeters (mm^3) should be reported in an expedited way to the sponsor. To add language that if there was no reportable platelet count within 14 days, investigator would contact the patient to hold dosing until a new platelet count was obtained and reviewed. To add language that all platelet count results would be promptly reviewed by the investigator to ensure that the count had not met the stopping rule, and to determine whether the rate of decline was suggestive that the subject could be approaching the dose pause rule of 75,000/mm^3. To add 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. To change platelet dose pause/stopping rule from 50,000/mm^3 to 75,000/mm^3. To add that when platelet count returned to ≥ 100,000/mm^3 dosing may be continued but at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg/week and only if approved by the sponsor medical monitor. To add language that in event of any platelet count less than 25,000/mm^3, or a platelet count less than 50,000/mm^3 that occurred while the subject was dosed at 300 mg every 2 weeks or 150 mg/week, then dosing of a subject with study drug would be stopped permanently. Platelet count would be monitored daily until 2 successive values showed improvement then monitored every 2–3 days until platelet count was stable. To add generic name, volanesorsen, for ISIS 304801. To add new name of the Sponsor, Ionis Pharmaceuticals, and collaborators, Akcea Therapeutics.
08 August 2016	To specify additional platelet monitoring and stopping rules. To provide updated blinded safety data from the ongoing studies of volanesorsen. To amend the inclusion and exclusion criteria to better identify subjects with FPL and Type 2 diabetes at entry into the study who could benefit from the study drug. To revise the stratification strategy for the study. To change the order of the secondary endpoints (i.e., elevate the importance of glycemic-related endpoints). To update the corresponding statistical analysis sections. To add a 12-month open-label extension period within this study instead of a separate elective study.
17 April 2017	To update the platelet safety monitoring rules.
22 August 2017	To revise the diabetic criteria consistent with more current guidelines, an increased HbA1c threshold of 12%, and require all subjects to be on antidiabetic agents (oral or injectable). To allow subjects in Group 1 and Group 2 subjects with TG levels of 200 mg/dL or greater to participate in the study, with evidence of fatty liver. To revise secondary endpoints (i.e., added patient-reported outcomes as a secondary endpoint, assessment of hepatic steatoses as first secondary endpoint, added reductions in pain medication or mood medication use). To add an option for an additional 52 weeks of open-label dosing. To add scoring of disease burden. To clarify actions to be taken regarding events of documented hypoglycemia and hyperglycemia. To add allowance for unblinding of TG values to both investigators and subject after 13 weeks on the open-label period of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The Sponsor decided to terminate the study early at a time point when sufficient data had been accumulated to inform a decision on further development of volanesorsen in subjects with FPL.

Notes: