

**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 | <ul style="list-style-type: none">• 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-APOCIIRx |
| 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-APOCIIRx |
| 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 interfere) 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 interfere) 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

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: | |
| <p>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.</p> | |
| 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 occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Reproductive system and breast disorders | | | |
| Menstrual disorder subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Vulval disorder subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 7 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 21 (9.52%) 7 | 0 / 7 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 2 | 0 / 7 (0.00%) 0 |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Sinus congestion subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 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 occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Atrioventricular block second degree subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 3 / 21 (14.29%) 3 | 1 / 7 (14.29%) 1 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Dysstasia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 4 / 21 (19.05%) 8 | 0 / 7 (0.00%) 0 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Syncope | | | |

| | | | |
|--|---------------------|---------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 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 occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 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 occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Xanthoma subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Chromaturia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Dysuria subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Micturition urgency subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Nephrolithiasis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 21 (4.76%) 1 | 0 / 7 (0.00%) 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 occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Surgical and medical procedures Asthma prophylaxis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Cardiac pacemaker insertion subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Sinus operation subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Chills subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Injection site bruising subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 12 (25.00%) 7 | 0 / 12 (0.00%) 0 |
| Injection site discolouration subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 12 (0.00%) 0 |

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

| | | | |
|--|---------------------|----------------------|----------------------|
| Injection site warmth subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 2 | 1 / 12 (8.33%) 1 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 12 (16.67%) 3 | 2 / 12 (16.67%) 3 |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 3 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Reproductive system and breast disorders Menstrual disorder subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Vulval disorder subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 12 (16.67%) 2 | 0 / 12 (0.00%) 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 occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Rheumatoid factor increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Synovial fluid white blood cells positive subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Urine albumin/creatinine ratio increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Urine protein, quantitative subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 12 (8.33%) 1 |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 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 occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Splinter subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Congenital, familial and genetic disorders | | | |
| Muscular dystrophy subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Cardiac disorders | | | |
| Atrioventricular block complete subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Atrioventricular block second degree subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Dysstasia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 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 occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 2 |
| Proteinuria subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Thyroid mass subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Muscle fatigue subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 2 | 1 / 12 (8.33%) 1 |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 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 occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Metabolism and nutrition disorders | | | |
| Appetite disorder subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 2 | 1 / 12 (8.33%) 1 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 2 |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 12 (16.67%) 14 | 2 / 12 (16.67%) 2 |
| Insulin resistance subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 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 $\leq 50,000/\text{cubic millimeters (mm}^3\text{)}$ 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 $75,000/\text{mm}^3$. 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 $50,000/\text{mm}^3$ to $75,000/\text{mm}^3$. To add that when platelet count returned to $\geq 100,000/\text{mm}^3$ 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 $25,000/\text{mm}^3$, or a platelet count less than $50,000/\text{mm}^3$ 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: