



Clinical trial results:

A Multicenter, Open-Label, Extension Study to Evaluate the Long-term Safety and Efficacy of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Completed a Prior Clinical Study with Patisiran

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2014-003877-40 |
| Trial protocol | ES SE PT DE NL GB CY IT |
| Global end of trial date | 23 November 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 02 December 2023 |
| First version publication date | 02 December 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | ALN-TTR02-006 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02510261 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Alnylam Pharmaceuticals, Inc. |
| Sponsor organisation address | 675 West Kendall Street, Cambridge, United States, 02142 |
| Public contact | Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com |
| Scientific contact | Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.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 | 23 November 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 November 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of long-term dosing with patisiran in subjects with hereditary transthyretin (TTR)-mediated amyloidosis (hATTR).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 16 July 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Cyprus: 3 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | France: 38 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Japan: 10 |
| Country: Number of subjects enrolled | Korea, Republic of: 8 |
| Country: Number of subjects enrolled | Mexico: 13 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Portugal: 17 |
| Country: Number of subjects enrolled | Sweden: 13 |
| Country: Number of subjects enrolled | Turkey: 5 |
| Country: Number of subjects enrolled | Taiwan: 14 |
| Country: Number of subjects enrolled | United States: 35 |
| Worldwide total number of subjects | 211 |
| EEA total number of subjects | 116 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 108 |
| From 65 to 84 years | 103 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at investigational sites in Asia, Europe, Canada, the United Kingdom, and the United States from 16 July 2015 to 23 November 2022.

Pre-assignment

Screening details:

A total of 211 subjects who completed either ALN-TTR02-003 (2013-001644-65) or ALN-TTR02-004 (2013-002987-17) studies were enrolled into the study to receive at least 1 dose of patisiran.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Prior Placebo Group of Study 004 |

Arm description:

Subjects who received placebo and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 milligrams per kilogram (mg/kg) patisiran intravenously (IV) once every 3 weeks (Q3W) up to 65.5 months.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Patisiran |
| Investigational medicinal product code | |
| Other name | ALN-TTR02 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 0.3 mg/kg patisiran Q3W up to 65.5 months.

| | |
|------------------|------------------------------------|
| Arm title | Prior Patisiran Group of Study 004 |
|------------------|------------------------------------|

Arm description:

Subjects who received patisiran and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 66.9 months.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Patisiran |
| Investigational medicinal product code | |
| Other name | ALN-TTR02 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 0.3 mg/kg patisiran Q3W up to 66.9 months.

| | |
|------------------|------------------------------------|
| Arm title | Prior Patisiran Group of Study 003 |
|------------------|------------------------------------|

Arm description:

Subjects who received patisiran and completed parent study ALN-TTR02-003 (2013-001644-65) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 61.4 months.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Patisiran |
| Investigational medicinal product code | |
| Other name | ALN-TTR02 |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 0.3 mg/kg patisiran Q3W up to 61.4 months.

| Number of subjects in period 1 | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 |
|---------------------------------------|----------------------------------|------------------------------------|------------------------------------|
| Started | 49 | 137 | 25 |
| Completed | 21 | 95 | 22 |
| Not completed | 28 | 42 | 3 |
| Physician decision | 1 | 5 | - |
| Adverse Event | 5 | 8 | - |
| Death | 19 | 19 | - |
| Withdrawal by Subject | 3 | 10 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Prior Placebo Group of Study 004 |
|-----------------------|----------------------------------|

Reporting group description:

Subjects who received placebo and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 milligrams per kilogram (mg/kg) patisiran intravenously (IV) once every 3 weeks (Q3W) up to 65.5 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 004 |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 66.9 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 003 |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-003 (2013-001644-65) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 61.4 months.

| Reporting group values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 |
|---|----------------------------------|------------------------------------|------------------------------------|
| Number of subjects | 49 | 137 | 25 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 63.5 ± 11.02 | 61.0 ± 12.10 | 58.5 ± 15.09 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 35 | 8 |
| Male | 37 | 102 | 17 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 9 | 16 | 2 |
| Not Hispanic or Latino | 39 | 121 | 23 |
| Unknown or Not Reported | 1 | 0 | 0 |
| Race Units: Subjects | | | |
| Asian | 14 | 23 | 0 |
| Black/African or African American | 0 | 4 | 0 |
| White/Caucasian | 34 | 107 | 25 |
| Other | 0 | 2 | 0 |
| More than One Race | 0 | 1 | 0 |
| Missing | 1 | 0 | 0 |
| Serum TTR Level | | | |
| Number analysed: Prior Placebo Group of Study 004 (n=40), Prior Patisiran Group of Study 004 (n=128), and Prior Patisiran Group of Study 003 (n=24) | | | |
| Units: mg/L arithmetic mean standard deviation | 185.689 ± 56.2895 | 53.010 ± 43.1782 | 76.905 ± 47.9088 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 211 | | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 55 | | |
| Male | 156 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 27 | | |
| Not Hispanic or Latino | 183 | | |
| Unknown or Not Reported | 1 | | |
| Race Units: Subjects | | | |
| Asian | 37 | | |
| Black/African or African American | 4 | | |
| White/Caucasian | 166 | | |
| Other | 2 | | |
| More than One Race | 1 | | |
| Missing | 1 | | |
| Serum TTR Level | | | |
| Number analysed: Prior Placebo Group of Study 004 (n=40), Prior Patisiran Group of Study 004 (n=128), and Prior Patisiran Group of Study 003 (n=24) | | | |
| Units: mg/L arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Prior Placebo Group of Study 004 |
|-----------------------|----------------------------------|

Reporting group description:

Subjects who received placebo and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 milligrams per kilogram (mg/kg) patisiran intravenously (IV) once every 3 weeks (Q3W) up to 65.5 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 004 |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 66.9 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 003 |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-003 (2013-001644-65) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 61.4 months.

Primary: Percentage of Subjects With Adverse Events (AEs) Leading to Study Discontinuation

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Adverse Events (AEs) Leading to Study Discontinuation ^[1] |
|-----------------|--|

End point description:

AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Safety analysis set included all the enrolled subjects who received at least 1 dose of patisiran in this study. Percentages are rounded off to the nearest decimal point.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

First dose up to 28 days after last dose of study drug (approximately 5.6 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned for this endpoint.

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|-------------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 49.0 | 16.8 | 0.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Total Neuropathy Impairment Score (NIS) at Year 5

| | |
|-----------------|---|
| End point title | Change From Baseline in the Total Neuropathy Impairment Score (NIS) at Year 5 |
|-----------------|---|

End point description:

The NIS assessment is a 244-point composite measure of neurologic impairment which includes a physical exam of lower limbs, upper limbs, and cranial nerves to assess the components: motor strength/weakness (NIS-W), reflexes (NIS-R), and sensation (NIS-S). NIS total score is obtained by combining all the component scores, ranging from 0 to 244. Higher scores represent a greater severity of disease. A positive change from baseline indicates the worsening of neuropathy. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 81.47 (± 41.674) | 62.26 (± 37.875) | 35.48 (± 28.686) | |
| Change From Baseline at Year 5 (n=21,92,22) | 11.45 (± 16.566) | 10.72 (± 13.654) | 11.18 (± 17.554) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Total Modified NIS (mNIS +7) Composite Score at Year 3

| | |
|-----------------|--|
| End point title | Change From Baseline in the Total Modified NIS (mNIS +7) Composite Score at Year 3 |
|-----------------|--|

End point description:

The mNIS+7 is a composite measure of neurologic impairment which includes the following components: physical exam of lower limbs, upper limbs, and cranial nerves to assess motor strength/weakness (192 points), reflexes (20 points), electrophysiologic measurement of small and large nerve fiber function (10 points), sensory testing (80 points), and postural blood pressure (2 points). The total mNIS+7 composite score is obtained by combining all the component scores, ranging from 0 (no impairment) to 304 (maximum impairment). A negative change from baseline indicates an improvement in neuropathy. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 3

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 101.07 (± 43.774) | 74.72 (± 42.584) | 45.66 (± 31.640) | |
| Change From Baseline at Year 3 (n= 27, 105, 25) | -6.69 (± 3.389) | 8.07 (± 1.874) | 5.46 (± 2.450) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the NIS+7 Total Score at Week 52

| | |
|------------------------|--|
| End point title | Change From Baseline in the NIS+7 Total Score at Week 52 |
| End point description: | <p>The NIS+7 provides additional, objective measures of nerve fiber function and autonomic nerve function in subjects with diabetic neuropathy. The NIS+7 includes the full NIS, sum of 5 nerve conduction studies (NCS) (Sural sensory nerve action potential [SNAP], tibial motor nerve distal latency, peroneal compound motor action potential [CMAP], motor nerve conduction velocity, motor nerve distal latency), vibration detection threshold, and pulse rate response to deep breathing. The total NIS+7 score is obtained by combining all the component scores, ranging from 0 (no impairment) to 270 points (maximum impairment). A positive change from baseline indicates worsening. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.</p> |
| End point type | Secondary |
| End point timeframe: | Baseline, Week 52 |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 98.42 (± 42.281) | 78.74 (± 39.417) | 49.66 (± 31.319) | |
| Change From Baseline at Week 52 (n=38, 126, 25) | 1.44 (± 2.061) | 1.49 (± 0.894) | 3.23 (± 2.616) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) Questionnaire Total Score at Year 5

| | |
|--|--|
| End point title | Change From Baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) Questionnaire Total Score at Year 5 |
| End point description: The Norfolk QoL-DN questionnaire is a standardised 47-item patient-reported endpoint, sensitive to the perception of the effects of diabetic neuropathy by the subject. The scores range from -4 (best possible QOL) to 136 (worst possible QOL). A negative change from baseline represents improved QOL. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint. '9999' indicates that the standard deviation (SD) cannot be estimated for one subject. | |
| End point type | Secondary |
| End point timeframe: Baseline, Year 5 | |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|--|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 1 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 72.7 (± 28.10) | 54.5 (± 30.87) | 34.0 (± 9999) | |
| Change From Baseline at Year 5 (n=21, 94, 1) | 3.3 (± 13.91) | 4.5 (± 17.19) | -18.0 (± 9999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the EuroQOL-5 Dimensions-5 Levels (EQ-5D-5L) Index Score at Year 5

| | |
|---|--|
| End point title | Change From Baseline in the EuroQOL-5 Dimensions-5 Levels (EQ-5D-5L) Index Score at Year 5 |
| End point description: The EQ-5D-5L is a patient-reported measure of QoL based on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The overall score is rated on a scale from 0 (worst) to 1 (no impairment). Higher scores indicate a higher QoL. A negative change from baseline indicates worsening of QoL. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint. | |
| End point type | Secondary |
| End point timeframe: Baseline, Year 5 | |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 0.4614 (± 0.03347) | 0.6444 (± 0.01856) | 0.7663 (± 0.03336) | |
| Change From Baseline at Year 5 (n=21, 94, 21) | 0.0361 (± 0.04017) | -0.0548 (± 0.01767) | -0.0166 (± 0.02363) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the EuroQoL Visual Analogue Scale (EQ-VAS) Score at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the EuroQoL Visual Analogue Scale (EQ-VAS) Score at Year 5 |
|-----------------|--|

End point description:

EQ-VAS measures the subject's self-rated health on a vertical scale evaluated on a scale of 0 ("worst health you can imagine") to 100 ("best health you can imagine"). Higher scores indicate a higher QoL. A negative change from baseline indicates worsening of QoL. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 46.0 (± 2.86) | 57.8 (± 1.82) | 69.1 (± 4.20) | |
| Change From Baseline at Year 5 (n=21, 94, 22) | 9.3 (± 5.03) | -1.5 (± 1.43) | 1.5 (± 2.99) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Composite Autonomic Symptom Score (COMPASS 31) Total Score at Week 52

| | |
|-----------------|---|
| End point title | Change From Baseline in the Composite Autonomic Symptom Score (COMPASS 31) Total Score at Week 52 |
|-----------------|---|

End point description:

COMPASS 31 questionnaire measures autonomic symptoms in subjects with neuropathy. The questionnaire consists of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, secretomotor, gastrointestinal, bladder, and pupillomotor). COMPASS 31 is measured on a scale from 0 to 100, with 100 representing maximum impairment. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 33.92 (± 18.185) | 25.37 (± 17.010) | 15.93 (± 15.116) | |
| Change From Baseline at Week 52 (n=38, 126, 25) | -3.70 (± 12.957) | 0.37 (± 12.041) | -1.24 (± 1.595) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Modified Body Mass Index (mBMI) at Year 5

| | |
|-----------------|---|
| End point title | Change From Baseline in the Modified Body Mass Index (mBMI) at Year 5 |
|-----------------|---|

End point description:

Nutritional status of subjects was evaluated using the mBMI, calculated as BMI (kilograms per square metre [kg/m²]) multiplied by the concentration of serum albumin (grams per litre [g/L]). A positive change from baseline indicates improvement in nutritional status. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: kg.g/m ² .L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 881.8 (± 219.10) | 970.7 (± 218.40) | 1002.3 (± 173.80) | |
| Change From Baseline at Year 5 (n=20, 84, 22) | 74.0 (± 146.85) | 31.6 (± 119.28) | 77.8 (± 91.36) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Rasch-built Overall Disability Scale (R-ODS) at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Rasch-built Overall Disability Scale (R-ODS) at Year 5 |
|-----------------|--|

End point description:

The R-ODS is a 24-item patient-reported questionnaire that specifically captures activity and social participation limitations. It measures the level of disability on a scale of 0 (worst) to 48 (best, no limitations), higher score indicates a better outcome. A negative change from baseline indicates worsening of disability. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 20.3 (± 12.74) | 29.7 (± 12.56) | 36.7 (± 10.29) | |
| Change From Baseline at Year 5 (n=20, 93, 22) | -2.9 (± 5.25) | -4.1 (± 6.78) | -2.7 (± 3.60) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the NIS+7 Component: NIS-Weakness (NIS-W) Score at Year 5

| | |
|---|---|
| End point title | Change From Baseline in the NIS+7 Component: NIS-Weakness (NIS-W) Score at Year 5 |
| End point description: The NIS+7 provides additional, objective measures of nerve fiber function and autonomic nerve function in subjects with diabetic neuropathy. The NIS+7 includes the full NIS (NIS-W, NIS-R, NIS-S), sum of 5 nerve conduction studies (NCS) (Sural SNAP, tibial motor nerve distal latency, peroneal CMAP, motor nerve conduction velocity, motor nerve distal latency), vibration detection threshold, and pulse rate response to deep breathing. NIS-W is a measure of motor strength, comprised of cranial nerve and both upper and lower limb motor assessments. The score ranges from 0 to 192. A higher score indicates greater severity of disease. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed' indicates the number of subjects with data available for analysis at specified timepoint. | |
| End point type | Secondary |
| End point timeframe: Baseline, Year 5 | |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 47.01 (± 31.323) | 33.26 (± 27.434) | 15.02 (± 17.988) | |
| Change From Baseline at Year 5 (n=21, 92, 22) | 9.10 (± 13.297) | 7.37 (± 11.707) | 6.97 (± 13.235) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the 10-metre Walk Test (10-MWT) Speed at Year 5

| | |
|--|---|
| End point title | Change From Baseline in the 10-metre Walk Test (10-MWT) Speed at Year 5 |
| End point description: 10-MWT is a measure of ambulatory ability and walk speed. It measures the speed (in metres per second [m/s]) of a subject to walk 10 metres. A negative change from baseline represents decreased ambulatory ability. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed' indicates the number of subjects with data available for analysis at specified timepoint. | |
| End point type | Secondary |
| End point timeframe: Baseline, Year 5 | |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: m/s | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 0.538 (± 0.0553) | 0.851 (± 0.0422) | 1.262 (± 0.0826) | |
| Change From Baseline at Year 5 (n=21, 92, 22) | 0.011 (± 0.0339) | -0.050 (± 0.0542) | -0.121 (± 0.0487) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Hand Grip Strength at Week 52

| | |
|-----------------|---|
| End point title | Change From Baseline in the Hand Grip Strength at Week 52 |
|-----------------|---|

End point description:

Hand grip strength was measured by dynamometer. Grip strength in the dominant arm is a measure of motor function, with a higher grip strength indicating better motor function. The mean change from baseline in the hand grip strength was reported. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: kg | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 10.23 (± 1.293) | 18.03 (± 1.081) | 27.86 (± 2.626) | |
| Change From Baseline at Week 52 (n=38, 125, 25) | 0.14 (± 0.461) | -0.34 (± 0.615) | -0.28 (± 0.807) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change From Baseline in the Polyneuropathy Disability (PND) Stage

| | |
|-----------------|---|
| End point title | Number of Subjects With Change From Baseline in the |
|-----------------|---|

End point description:

PND measures changes in the ambulatory ability including the need of walking aids on the following stages: 0 (no symptoms), I (sensory disturbances but preserved walking capability), II (impaired walking capability but ability to walk without a stick or crutches), IIIA (walking with help of 1 stick/crutch), IIIB (with help of 2 sticks/crutches), and IV (confined to wheelchair or bedridden). Lower scores indicate greater ambulatory function. The number of subjects with change in the stage from baseline was reported as: Improved or worsened. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 | 94 | 22 | |
| Units: subjects | | | | |
| Improved | 1 | 9 | 3 | |
| Worsened | 8 | 35 | 5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change From Baseline in the Familial Amyloidotic Polyneuropathy (FAP) Stage

| | |
|-----------------|---|
| End point title | Number of Subjects With Change From Baseline in the Familial Amyloidotic Polyneuropathy (FAP) Stage |
|-----------------|---|

End point description:

FAP measures changes in the ambulatory ability including the need of walking aids on the following stages: 0 (no symptoms), I (unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs), II (assistance with ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk), and III (wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs). Lower scores indicate greater ambulatory function. The number of subjects with change in the stage from baseline was reported as: Improved or worsened. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 | 93 | 22 | |
| Units: subjects | | | | |
| Improved | 0 | 3 | 1 | |
| Worsened | 5 | 13 | 2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change From Baseline in the New York Heart Association (NYHA) Classification

| | |
|-----------------|--|
| End point title | Number of Subjects With Change From Baseline in the New York Heart Association (NYHA) Classification |
|-----------------|--|

End point description:

NYHA classification grades severity of heart failure symptoms into following stages: I (no symptoms; ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea), II (symptoms with ordinary physical activity; walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea), III (symptoms with less than ordinary physical activity; walking 1-2 blocks on level and climbing more than 1 flight of stairs in normal conditions causes undue fatigue or dyspnea), IV (symptoms at rest; inability to carry on any physical activity without fatigue or dyspnea). The number of subjects with change in the stage from baseline was reported as: Improved or worsened. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|-----------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 87 | 21 | |
| Units: subjects | | | | |
| Improved | 2 | 13 | 1 | |
| Worsened | 4 | 18 | 4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Intraepidermal Nerve Fiber Density (IENFD) at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Intraepidermal Nerve Fiber |
|-----------------|--|

End point description:

IENFD (fibers/millimetre [mm]) is a measure for the pathologic evaluation of sensory and autonomic innervation. It is obtained by tandem 3 mm skin punch biopsies: one set of biopsies taken from the distal thigh (ENF, T) and one set from the distal lower leg (ENF, L). An increase in nerve fiber density suggests improvement, while a decrease in nerve fiber density suggests worsening. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|--|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 61 | 19 | |
| Units: fibers/mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Epidermal Nerve Fibers, Thigh (ENF, T): Baseline | 4.71 (± 5.249) | 5.41 (± 5.291) | 8.99 (± 10.027) | |
| ENF, T: Change From Baseline at Year 5 (n=2,15,11) | 0.28 (± 2.298) | -2.75 (± 3.126) | -5.53 (± 7.998) | |
| ENF, L: Baseline(n=13,60,18) | 0.47 (± 0.843) | 1.70 (± 3.183) | 3.66 (± 8.286) | |
| ENF, L: Change From Baseline at Year 5 (n=2,15,11) | -0.25 (± 0.495) | -1.31 (± 1.879) | -3.50 (± 8.428) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Sweat Gland Nerve Fiber Density (SGNFD) at Year 5

| | |
|-----------------|---|
| End point title | Change From Baseline in the Sweat Gland Nerve Fiber Density (SGNFD) at Year 5 |
|-----------------|---|

End point description:

SGNFD (metre/cubic millimetre [m/mm³]) is a measure for the pathologic evaluation of sensory and autonomic innervation. It is obtained by tandem 3 mm skin punch biopsies: one set of biopsies taken from the distal thigh (SGNF, T) and one set from the distal lower leg (SGNF, L). An increase in nerve fiber density suggests improvement, while a decrease in nerve fiber density suggests worsening. Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis of the specified parameter at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|--|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 59 | 19 | |
| Units: m/mm ³ | | | | |
| arithmetic mean (standard deviation) | | | | |
| SGNF, T: Baseline | 10.82 (± 6.638) | 9.67 (± 4.942) | 9.14 (± 4.802) | |
| SGNF, T: Change From Baseline at Year 5(n=2,14,10) | -0.56 (± 2.648) | -2.49 (± 5.636) | -3.29 (± 4.323) | |
| SGNF, L: Baseline (n=13,59,18) | 2.82 (± 3.363) | 4.99 (± 4.274) | 5.93 (± 4.355) | |
| SGNF, L: Change From Baseline at Year 5(n=2,15,9) | 1.43 (± 2.351) | -2.47 (± 3.605) | -1.31 (± 2.867) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Dermal Amyloid Burden at Year 5

| | |
|-----------------|---|
| End point title | Change From Baseline in the Dermal Amyloid Burden at Year 5 |
|-----------------|---|

End point description:

Dermal Amyloid Burden is a measure for the pathologic evaluation of sensory and autonomic innervation and reported as % congo red stain. It is obtained by tandem 3 mm skin punch biopsies: one set of biopsies taken from the distal thigh (AS, T) and one set from the distal lower leg (AS, L). Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis of the specified parameter at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 15 | 61 | 18 | |
| Units: percent congo red stain | | | | |
| arithmetic mean (standard deviation) | | | | |
| AS, T: Baseline | 8.163 (± 10.6544) | 8.205 (± 10.8725) | 5.908 (± 7.6646) | |
| AS, T: Change From Baseline at Year 5 (n=2,15,10) | -3.775 (± 5.3387) | -1.103 (± 7.5569) | -3.100 (± 5.7269) | |
| AS, L: Baseline (n=13,60,17) | 11.062 (± 10.4857) | 10.386 (± 12.3967) | 7.441 (± 8.5566) | |
| AS, L: Change From Baseline at Year 5 (n=2,15,10) | -7.475 (± 5.6922) | -2.793 (± 6.2309) | -3.935 (± 6.6372) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Cardiac Biomarker: Serum Troponin I at Year 5

| | |
|-----------------|---|
| End point title | Change From Baseline in the Cardiac Biomarker: Serum Troponin I at Year 5 |
|-----------------|---|

End point description:

Manifestations of cardiac amyloid involvement were assessed through measurement of serum levels of the cardiac biomarker: troponin (micrograms per litre [$\mu\text{g/L}$]). The troponin I values $<0.1 \mu\text{g/L}$ were imputed to 0.1 thus the actual changes cannot be calculated for values $<0.1 \mu\text{g/L}$. Full analysis set included all subjects who were enrolled in this study. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: $\mu\text{g/L}$ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.109 (\pm 0.0360) | 0.112 (\pm 0.0963) | 0.088 (\pm 0.0263) | |
| Change From Baseline at Year 5 (n= 18, 85, 22) | 0.546 (\pm 2.3345) | -0.005 (\pm 0.0244) | 0.014 (\pm 0.0277) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Cardiac Biomarker: N-terminal Prohormone of B-type Natriuretic Peptide (NT-proBNP) at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Cardiac Biomarker: N-terminal Prohormone of B-type Natriuretic Peptide (NT-proBNP) at Year 5 |
|-----------------|--|

End point description:

Manifestations of cardiac amyloid involvement were assessed through measurement of serum levels of the cardiac biomarker: NT-proBNP (nanograms per litre [ng/L]). Full analysis set included all subjects who were enrolled in this study. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: ng/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1957.649 (\pm 2731.3296) | 1017.217 (\pm 1558.7632) | 281.899 (\pm 421.9627) | |
| Change From Baseline at Year 5 (n=19, 84, 21) | -18.490 (\pm 910.2156) | 209.126 (\pm 487.2140) | 78.146 (\pm 266.1912) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: Average Peak Longitudinal Strain at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Echocardiogram Parameter: Average Peak Longitudinal Strain at Year 5 |
|-----------------|--|

End point description:

The echocardiogram parameters analysed included measures of systolic function: Average peak longitudinal strain (percentage [%]). Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 136 | 25 | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | -15.63 (\pm 3.348) | -15.96 (\pm 3.283) | -17.72 (\pm 4.079) | |
| Change From Baseline at Year 5 (n=21, 87, 22) | 3.43 (\pm 3.634) | 2.30 (\pm 3.300) | 1.62 (\pm 3.082) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: Left Ventricular (LV) Mass at Year 5

| | |
|------------------------|--|
| End point title | Change From Baseline in the Echocardiogram Parameter: Left Ventricular (LV) Mass at Year 5 |
| End point description: | The echocardiogram parameters analysed included measures of cardiac structure: LV mass (grams [g]). Full analysis set included all subjects who were enrolled in this study. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint. |
| End point type | Secondary |
| End point timeframe: | Baseline, Year 5 |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: grams | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 238.166 (\pm 74.0536) | 236.604 (\pm 85.8152) | 198.570 (\pm 89.1780) | |
| Change From Baseline at Year 5 (n=20, 89, 22) | 2.723 (\pm 52.1737) | -4.222 (\pm 48.2397) | -17.152 (\pm 50.9296) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: LV End-diastolic Volume at Year 5

| | |
|------------------------|--|
| End point title | Change From Baseline in the Echocardiogram Parameter: LV End-diastolic Volume at Year 5 |
| End point description: | The echocardiogram parameters analysed included measures of diastolic function: LV end-diastolic volume (millilitres [mL]). Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint. |
| End point type | Secondary |
| End point timeframe: | Baseline, Year 5 |

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|--------------------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 136 | 25 | |
| Units: mL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|-------------------------|-------------------------|--------------------------|--|
| Baseline | 80.591 (\pm 26.5862) | 83.616 (\pm 25.6990) | 107.818 (\pm 34.8418) | |
| Change From Baseline at Year 5 (n=21, 84, 21) | 7.173 (\pm 15.9316) | -1.279 (\pm 20.0305) | -11.710 (\pm 32.1329) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: LV Relative Wall Thickness at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Echocardiogram Parameter: LV Relative Wall Thickness at Year 5 |
|-----------------|--|

End point description:

The echocardiogram parameters analysed included measures of cardiac structure: LV relative wall thickness (ratio). Full analysis set included all subjects who were enrolled in this study. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.780 (\pm 0.1616) | 0.717 (\pm 0.1840) | 0.593 (\pm 0.1802) | |
| Change From Baseline at Year 5 (n=20, 89, 22) | -0.066 (\pm 0.1344) | -0.061 (\pm 0.1320) | -0.037 (\pm 0.0887) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: Mean LV Wall Thickness at Year 5

| | |
|-----------------|--|
| End point title | Change From Baseline in the Echocardiogram Parameter: Mean LV Wall Thickness at Year 5 |
|-----------------|--|

End point description:

The echocardiogram parameters analysed included measures of cardiac structure: Mean LV wall thickness (centimetre [cm]). Full analysis set included all subjects who were enrolled in this study. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 137 | 25 | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1.538 (± 0.2776) | 1.463 (± 0.3210) | 1.249 (± 0.3321) | |
| Change From Baseline at Year 5 (n=20, 89, 22) | -0.035 (± 0.1782) | -0.041 (± 0.1874) | -0.042 (± 0.1794) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Echocardiogram Parameter: Cardiac Output at Year 5

End point title Change From Baseline in the Echocardiogram Parameter: Cardiac Output at Year 5

End point description:

The echocardiogram parameters analysed included measures of systolic function: Cardiac output (litres per minute [L/min]). Full analysis set included all subjects who were enrolled in this study. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis at specified timepoint.

End point type Secondary

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|---|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 | 136 | 25 | |
| Units: L/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 3.547 (± 1.0373) | 3.840 (± 1.1748) | 4.873 (± 1.6902) | |
| Change From Baseline at Year 5 (n=21, 83, 21) | -0.010 (± 1.1551) | -0.283 (± 1.1012) | -0.594 (± 1.5476) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Serum TTR Levels at Year 5

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Serum TTR Levels at Year 5 |
|-----------------|--|

End point description:

Serum TTR was assessed using enzyme linked immunosorbent assay (ELISA). Pharmacodynamic (PD) analysis set included all subjects who received at least 1 dose of patisiran in this study and have had both baseline and at least 1 post-baseline PD assessment (either TTR or vitamin A). 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Year 5

| End point values | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 | |
|--------------------------------------|----------------------------------|------------------------------------|------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 80 | 21 | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -90.010 (\pm 7.4802) | -37.660 (\pm 35.2948) | -39.965 (\pm 56.5274) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose up to 28 days after last dose of study drug (approximately 5.6 years)

Adverse event reporting additional description:

Safety analysis set included all the enrolled subjects who received at least 1 dose of patisiran in this study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Prior Placebo Group of Study 004 |
|-----------------------|----------------------------------|

Reporting group description:

Subjects who received placebo and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 65.5 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 004 |
|-----------------------|------------------------------------|

Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-004 (2013-002987-17) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 66.9 months.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prior Patisiran Group of Study 003 |
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Reporting group description:

Subjects who received patisiran and completed parent study ALN-TTR02-003 (2013-001644-65) were enrolled to receive 0.3 mg/kg patisiran IV Q3W up to 61.4 months.

| Serious adverse events | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 |
|---|----------------------------------|------------------------------------|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 39 / 49 (79.59%) | 82 / 137 (59.85%) | 12 / 25 (48.00%) |
| number of deaths (all causes) | 21 | 22 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign Renal Neoplasm | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Bladder Cancer Recurrent | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone Cancer | | | |

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|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain Cancer Metastatic | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast Cancer | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Cholangiocarcinoma | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastric Cancer | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Hypopharyngeal Cancer | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Intraductal Proliferative Breast Lesion | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Invasive Ductal Breast Carcinoma | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Metastases to Lymph Nodes | | | |

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|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Metastases to Meninges | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Metastatic Malignant Melanoma | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic Syndrome | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Ocular Surface Squamous Neoplasia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oncocytoma | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic Shock | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neurogenic Shock | | | |

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|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Poor Peripheral Circulation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Shock | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Shock Haemorrhagic | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Varicose Vein | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Surgical and medical procedures | | | |
| Rehabilitation Therapy | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| General disorders and administration site conditions | | | |

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|---|----------------|-----------------|----------------|
| Asthenia | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest Discomfort | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extravasation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Gait Disturbance | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Generalised Oedema | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Implant Site Injury | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Polyp | | | |

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| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden Cardiac Death | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sudden Death | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Systemic Inflammatory Response Syndrome | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Social circumstances | | | |
| Disability | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 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 | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |

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| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Pulmonary Oedema | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Acute Respiratory Distress Syndrome | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Choking | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |

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| Pneumonia Aspiration | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Acidosis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 Arrest | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory Disorder | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Sleep Apnoea Syndrome | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional State | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conversion Disorder | | | |

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|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device Capturing Issue | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Device Physical Property Issue | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Device Power Source Issue | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Hepatobiliary disorders | | | |
| Bile Duct Stone | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Investigations | | | |

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| Blood Creatine Phosphokinase Increased | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Intraocular Pressure Increased | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Weight Decreased | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle Fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 2 / 25 (8.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burns Second Degree | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Facial Bones Fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |

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| Fibula Fracture | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Fractured Sacrum | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Hip Fracture | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 3 / 137 (2.19%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Joint Dislocation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Limb Injury | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Lower Limb Fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar Vertebral Fracture | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Overdose | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Rib Fracture | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Road Traffic Accident | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Stoma Site Extravasation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Tibia Fracture | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 2 / 25 (8.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic Haematoma | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Congenital, familial and genetic disorders | | | |
| Familial Amyloidosis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Hereditary Neuropathic Amyloidosis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|----------------|-----------------|----------------|
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 6 / 137 (4.38%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial Flutter | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 4 / 137 (2.92%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Atrial Tachycardia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular Block | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular Block Complete | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 3 / 137 (2.19%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular Block Second Degree | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Amyloidosis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 4 / 137 (2.92%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Arrest | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Cardiac Failure | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 137 (2.92%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac Flutter | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Cardiac Tamponade | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Cardiogenic Shock | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Conduction Disorder | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 3 / 137 (2.19%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary Artery Stenosis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Pulseless Electrical Activity | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Restrictive Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus Node Dysfunction | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Ventricular Arrhythmia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ventricular Tachycardia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Nervous system disorders | | | |
| Autonomic Nervous System Imbalance | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal Ganglia Infarction | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Carpal Tunnel Syndrome | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Cerebral Infarction | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 137 (2.92%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Hypoxic-ischaemic Encephalopathy | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Psychomotor Skills Impaired | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid Haemorrhage | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Syncope | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 137 (2.92%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Ear and labyrinth disorders | | | |
| Sudden Hearing Loss | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Vertigo Positional | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Corneal Perforation | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Deposit Eye | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye Haemorrhage | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Keratitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Retinal Artery Occlusion | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Retinal Detachment | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal Ischaemia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Rhegmatogenous Retinal Detachment | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulcerative Keratitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Vitreous Haemorrhage | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vitreous Opacities | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal Discomfort | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal Distension | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 1 / 137 (0.73%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea Haemorrhagic | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Faeces Pale | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Disorder | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Gastrointestinal Haemorrhage | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Ileus | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Inguinal Hernia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Large Intestine Polyp | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Nausea | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pancreatitis Acute | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Umbilical Hernia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Vomiting | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus Ulcer | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Skin Ulcer | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Calculus Bladder | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Chronic Kidney Disease | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| End Stage Renal Disease | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Neurogenic Bladder | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Urethral Haemorrhage | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Bladder Haemorrhage | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Retention | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|----------------|-----------------|----------------|
| Amyloid Arthropathy | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Foot Deformity | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Groin Pain | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 2 / 25 (8.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Rotator Cuff Syndrome | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 | | | |

| | | | |
|---|----------------|-----------------|----------------|
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 5 / 137 (3.65%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium Difficile Colitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gangrene | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes Zoster | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Infected Skin Ulcer | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Infusion Site Cellulitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parotitis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Pneumonia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 49 (4.08%) | 5 / 137 (3.65%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia Bacterial | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Septic Shock | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Soft Tissue Infection | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 4 / 137 (2.92%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 137 (1.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vascular Device Infection | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Viral Infection | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Wound Infection | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 | 2 / 49 (4.08%) | 0 / 137 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Electrolyte Imbalance | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Fluid Overload | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 0 / 137 (0.00%) | 0 / 25 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (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 |
| Metabolic Acidosis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 137 (0.73%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

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

| Non-serious adverse events | Prior Placebo Group of Study 004 | Prior Patisiran Group of Study 004 | Prior Patisiran Group of Study 003 |
|--|----------------------------------|------------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 49 (95.92%) | 135 / 137 (98.54%) | 25 / 25 (100.00%) |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 5 / 137 (3.65%) | 5 / 25 (20.00%) |
| occurrences (all) | 144 | 5 | 316 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 16 / 137 (11.68%) | 2 / 25 (8.00%) |
| occurrences (all) | 2 | 18 | 3 |
| Hypotension | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 16 / 137 (11.68%) | 0 / 25 (0.00%) |
| occurrences (all) | 3 | 18 | 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 8 / 137 (5.84%) | 2 / 25 (8.00%) |
| occurrences (all) | 3 | 14 | 2 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | 10 / 137 (7.30%) | 1 / 25 (4.00%) |
| occurrences (all) | 5 | 11 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 6 / 137 (4.38%) | 2 / 25 (8.00%) |
| occurrences (all) | 1 | 9 | 2 |
| Gait Disturbance | | | |

| | | | |
|---|-------------------------|--------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 1 / 137 (0.73%) 1 | 2 / 25 (8.00%) 2 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 4 / 137 (2.92%) 4 | 2 / 25 (8.00%) 2 |
| Oedema Peripheral subjects affected / exposed occurrences (all) | 15 / 49 (30.61%) 31 | 35 / 137 (25.55%) 69 | 6 / 25 (24.00%) 7 |
| Peripheral Swelling subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 6 | 8 / 137 (5.84%) 11 | 0 / 25 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 7 | 18 / 137 (13.14%) 27 | 3 / 25 (12.00%) 4 |
| Immune system disorders Infusion Related Reaction subjects affected / exposed occurrences (all) | 13 / 49 (26.53%) 160 | 17 / 137 (12.41%) 185 | 4 / 25 (16.00%) 18 |
| Reproductive system and breast disorders Benign Prostatic Hyperplasia subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 3 / 137 (2.19%) 3 | 1 / 25 (4.00%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 10 / 49 (20.41%) 16 | 20 / 137 (14.60%) 25 | 5 / 25 (20.00%) 6 |
| Dysphonia subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 7 / 137 (5.11%) 32 | 1 / 25 (4.00%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 9 | 6 / 137 (4.38%) 6 | 0 / 25 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 8 | 5 / 137 (3.65%) 5 | 1 / 25 (4.00%) 3 |
| Oropharyngeal Pain | | | |

| | | | |
|--|-----------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 4 / 137 (2.92%) 5 | 2 / 25 (8.00%) 2 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 5 / 137 (3.65%) 5 | 0 / 25 (0.00%) 0 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 4 | 1 / 137 (0.73%) 1 | 2 / 25 (8.00%) 2 |
| Depression subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 8 / 137 (5.84%) 8 | 2 / 25 (8.00%) 2 |
| Insomnia subjects affected / exposed occurrences (all) | 7 / 49 (14.29%) 54 | 11 / 137 (8.03%) 11 | 0 / 25 (0.00%) 0 |
| Investigations | | | |
| N-terminal Prohormone Brain Natriuretic Peptide Increased subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 3 / 137 (2.19%) 3 | 0 / 25 (0.00%) 0 |
| Weight Decreased subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 3 / 137 (2.19%) 6 | 0 / 25 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 8 / 137 (5.84%) 10 | 0 / 25 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 9 / 49 (18.37%) 27 | 33 / 137 (24.09%) 80 | 5 / 25 (20.00%) 5 |
| Foot Fracture subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 2 | 10 / 137 (7.30%) 10 | 0 / 25 (0.00%) 0 |
| Ligament Sprain subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 10 / 137 (7.30%) 11 | 1 / 25 (4.00%) 1 |
| Limb Injury | | | |

| | | | |
|---|------------------------|-------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 6 | 14 / 137 (10.22%) 16 | 6 / 25 (24.00%) 15 |
| Post-traumatic Pain subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 5 / 137 (3.65%) 5 | 2 / 25 (8.00%) 2 |
| Skin Abrasion subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 9 / 137 (6.57%) 14 | 0 / 25 (0.00%) 0 |
| Thermal Burn subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 9 | 11 / 137 (8.03%) 19 | 1 / 25 (4.00%) 1 |
| Traumatic Haematoma subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 9 / 137 (6.57%) 16 | 2 / 25 (8.00%) 3 |
| Cardiac disorders | | | |
| Arrhythmia subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 1 / 137 (0.73%) 1 | 0 / 25 (0.00%) 0 |
| Atrial Fibrillation subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 14 / 137 (10.22%) 23 | 0 / 25 (0.00%) 0 |
| Atrial Flutter subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 2 / 137 (1.46%) 2 | 2 / 25 (8.00%) 3 |
| Cardiac Failure subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | 3 / 137 (2.19%) 5 | 2 / 25 (8.00%) 2 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 11 / 49 (22.45%) 31 | 21 / 137 (15.33%) 28 | 1 / 25 (4.00%) 1 |
| Headache subjects affected / exposed occurrences (all) | 11 / 49 (22.45%) 19 | 19 / 137 (13.87%) 33 | 1 / 25 (4.00%) 4 |
| Neuralgia | | | |

| | | | |
|---|----------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 4 | 12 / 137 (8.76%) 83 | 2 / 25 (8.00%) 2 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 4 / 137 (2.92%) 4 | 2 / 25 (8.00%) 2 |
| Sciatica subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 9 | 8 / 137 (5.84%) 8 | 1 / 25 (4.00%) 2 |
| Somnolence subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | 7 / 137 (5.11%) 10 | 0 / 25 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 6 | 11 / 137 (8.03%) 14 | 2 / 25 (8.00%) 2 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 7 / 49 (14.29%) 9 | 10 / 137 (7.30%) 10 | 2 / 25 (8.00%) 3 |
| Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 2 | 0 / 137 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Vertigo subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 15 / 137 (10.95%) 18 | 4 / 25 (16.00%) 4 |
| Vertigo Positional subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 3 / 137 (2.19%) 4 | 2 / 25 (8.00%) 3 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 6 | 14 / 137 (10.22%) 17 | 5 / 25 (20.00%) 5 |
| Conjunctival Haemorrhage subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 5 | 4 / 137 (2.92%) 4 | 1 / 25 (4.00%) 1 |
| Visual Impairment | | | |

| | | | |
|--|-------------------------|--------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 1 / 137 (0.73%) 1 | 2 / 25 (8.00%) 3 |
| Gastrointestinal disorders | | | |
| Abdominal Discomfort subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 3 / 137 (2.19%) 8 | 0 / 25 (0.00%) 0 |
| Abdominal Pain subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 10 / 137 (7.30%) 14 | 1 / 25 (4.00%) 1 |
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 9 | 4 / 137 (2.92%) 5 | 1 / 25 (4.00%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 9 / 49 (18.37%) 11 | 19 / 137 (13.87%) 42 | 3 / 25 (12.00%) 3 |
| Dental Caries subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 5 / 137 (3.65%) 6 | 4 / 25 (16.00%) 4 |
| Diarrhoea subjects affected / exposed occurrences (all) | 22 / 49 (44.90%) 102 | 35 / 137 (25.55%) 152 | 3 / 25 (12.00%) 3 |
| Dry Mouth subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | 3 / 137 (2.19%) 3 | 0 / 25 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 2 / 137 (1.46%) 2 | 0 / 25 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 3 / 137 (2.19%) 3 | 0 / 25 (0.00%) 0 |
| Gastritis subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 5 | 7 / 137 (5.11%) 7 | 0 / 25 (0.00%) 0 |
| Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 5 / 137 (3.65%) 5 | 2 / 25 (8.00%) 3 |

| | | | |
|--|------------------|-------------------|-----------------|
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 7 / 137 (5.11%) | 0 / 25 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Nausea | | | |
| subjects affected / exposed | 10 / 49 (20.41%) | 22 / 137 (16.06%) | 3 / 25 (12.00%) |
| occurrences (all) | 22 | 49 | 3 |
| Toothache | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 8 / 137 (5.84%) | 2 / 25 (8.00%) |
| occurrences (all) | 4 | 10 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 49 (10.20%) | 14 / 137 (10.22%) | 3 / 25 (12.00%) |
| occurrences (all) | 8 | 21 | 5 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus Ulcer | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 7 / 137 (5.11%) | 0 / 25 (0.00%) |
| occurrences (all) | 8 | 8 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 2 / 137 (1.46%) | 2 / 25 (8.00%) |
| occurrences (all) | 3 | 2 | 2 |
| Eczema | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 5 / 137 (3.65%) | 0 / 25 (0.00%) |
| occurrences (all) | 4 | 9 | 0 |
| Erythema | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 8 / 137 (5.84%) | 1 / 25 (4.00%) |
| occurrences (all) | 7 | 36 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 5 / 137 (3.65%) | 0 / 25 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| Rash | | | |
| subjects affected / exposed | 3 / 49 (6.12%) | 12 / 137 (8.76%) | 1 / 25 (4.00%) |
| occurrences (all) | 3 | 13 | 2 |
| Skin Lesion | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 2 / 137 (1.46%) | 2 / 25 (8.00%) |
| occurrences (all) | 2 | 2 | 2 |
| Skin Ulcer | | | |

| | | | |
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| subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 6 | 7 / 137 (5.11%) 13 | 3 / 25 (12.00%) 4 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 2 / 137 (1.46%) 2 | 1 / 25 (4.00%) 1 |
| Dysuria subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 8 / 137 (5.84%) 8 | 1 / 25 (4.00%) 1 |
| Haematuria subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 4 | 9 / 137 (6.57%) 12 | 0 / 25 (0.00%) 0 |
| Renal Failure subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 137 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Urinary Retention subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 4 | 3 / 137 (2.19%) 3 | 2 / 25 (8.00%) 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 11 | 15 / 137 (10.95%) 16 | 2 / 25 (8.00%) 2 |
| Back Pain subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 18 | 21 / 137 (15.33%) 32 | 4 / 25 (16.00%) 4 |
| Muscle Spasms subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 19 | 13 / 137 (9.49%) 19 | 2 / 25 (8.00%) 2 |
| Musculoskeletal Pain subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 3 | 12 / 137 (8.76%) 14 | 3 / 25 (12.00%) 5 |
| Myalgia subjects affected / exposed occurrences (all) | 7 / 49 (14.29%) 7 | 4 / 137 (2.92%) 5 | 1 / 25 (4.00%) 1 |
| Neck Pain | | | |

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| subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 4 / 137 (2.92%) 4 | 0 / 25 (0.00%) 0 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 3 | 5 / 137 (3.65%) 5 | 2 / 25 (8.00%) 2 |
| Pain in Extremity subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 13 | 29 / 137 (21.17%) 38 | 4 / 25 (16.00%) 4 |
| Tendonitis subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 2 / 137 (1.46%) 2 | 2 / 25 (8.00%) 2 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 7 / 137 (5.11%) 12 | 1 / 25 (4.00%) 3 |
| COVID-19 subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 13 / 137 (9.49%) 13 | 0 / 25 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 9 / 137 (6.57%) 13 | 0 / 25 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 7 / 137 (5.11%) 10 | 0 / 25 (0.00%) 0 |
| Erysipelas subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 5 / 137 (3.65%) 6 | 3 / 25 (12.00%) 4 |
| Eye Infection subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 4 | 0 / 137 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Fungal Skin Infection subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 4 / 137 (2.92%) 5 | 2 / 25 (8.00%) 3 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 8 / 137 (5.84%) 9 | 0 / 25 (0.00%) 0 |

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| Infected Skin Ulcer subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 1 / 137 (0.73%) 2 | 3 / 25 (12.00%) 8 |
| Influenza subjects affected / exposed occurrences (all) | 6 / 49 (12.24%) 10 | 18 / 137 (13.14%) 20 | 4 / 25 (16.00%) 4 |
| Localised Infection subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 2 / 137 (1.46%) 2 | 2 / 25 (8.00%) 3 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 9 / 49 (18.37%) 26 | 28 / 137 (20.44%) 40 | 8 / 25 (32.00%) 20 |
| Respiratory Tract Infection subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 3 | 3 / 137 (2.19%) 4 | 3 / 25 (12.00%) 4 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 9 / 137 (6.57%) 10 | 1 / 25 (4.00%) 2 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 5 / 137 (3.65%) 6 | 2 / 25 (8.00%) 4 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 1 / 137 (0.73%) 1 | 3 / 25 (12.00%) 4 |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 21 / 137 (15.33%) 31 | 1 / 25 (4.00%) 1 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 16 / 49 (32.65%) 50 | 28 / 137 (20.44%) 89 | 5 / 25 (20.00%) 6 |
| Wound Infection subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 1 / 137 (0.73%) 1 | 2 / 25 (8.00%) 3 |
| Metabolism and nutrition disorders Decreased Appetite | | | |

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|--|-----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 8 / 137 (5.84%) 8 | 0 / 25 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | 7 / 137 (5.11%) 8 | 1 / 25 (4.00%) 1 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 7 / 49 (14.29%) 10 | 3 / 137 (2.19%) 3 | 1 / 25 (4.00%) 1 |
| Vitamin D Deficiency subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 4 / 137 (2.92%) 4 | 3 / 25 (12.00%) 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 08 September 2015 | Modified the premedication regimen as some subjects on this premedication regimen for an extended amount of time in Study ALN-TTR02-003 (2013-001644-65) reported recurrent episodes of flushing after the infusion that the Investigator(s) reported as an infusion related reaction (IRR) and/or related to the premedication dexamethasone. |
| 05 January 2017 | Added the Columbia-Suicide Severity Rating Scale (C-SSRS) to the study assessments, which was inadvertently left out of previous versions of the protocol. The inclusion of the C-SSRS addresses a regulatory requirement to prospectively assess suicidality in clinical trials involving all drugs for neurological indications. |
| 28 March 2018 | Expanded the collection of efficacy assessments beyond the current 52-week annual (Year 1) visit in the Schedule of Assessments. The additional efficacy assessment timepoints were added in order to better evaluate the long-term efficacy of patisiran. |
| 26 October 2018 | Recommended lowering the premedication corticosteroid dose for subjects who have tolerated well 3 or more infusions of patisiran with their current corticosteroid premedication regimen (ie, the subject has not had infusion related reactions during the past 3 or more infusions). This change was implemented since subjects who are tolerating patisiran infusions may benefit from corticosteroid reduction to avoid potential side effects associated with long-term corticosteroid use. |
| 11 May 2020 | Incorporated urgent safety measures (USMs) that were communicated to Investigators in a Dear Investigator Letter dated 09 April 2020 to ensure the safety of study subjects while minimizing risks to study integrity amid the COVID-19 pandemic. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported