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	63.5	61.0	58.5
standard deviation	± 11.02	± 12.10	± 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	185.689	53.010	76.905
standard deviation	± 56.2895	± 43.1782	± 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:

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.

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/m^2]) 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

	Polyneuropathy Disability (PND) Stage

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

	Density (IENFD) at Year 5

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/mm^3]) 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 [µg/L]). The troponin I values <0.1 µg/L were imputed to 0.1 thus the actual changes cannot be calculated for values <0.1 µg/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: µg/L				
arithmetic mean (standard deviation)				
Baseline	0.109 (± 0.0360)	0.112 (± 0.0963)	0.088 (± 0.0263)	
Change From Baseline at Year 5 (n= 18, 85, 22)	0.546 (± 2.3345)	-0.005 (± 0.0244)	0.014 (± 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 (± 2731.3296)	1017.217 (± 1558.7632)	281.899 (± 421.9627)	
Change From Baseline at Year 5 (n=19, 84, 21)	-18.490 (± 910.2156)	209.126 (± 487.2140)	78.146 (± 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 (± 3.348)	-15.96 (± 3.283)	-17.72 (± 4.079)	
Change From Baseline at Year 5 (n=21, 87, 22)	3.43 (± 3.634)	2.30 (± 3.300)	1.62 (± 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 (± 74.0536)	236.604 (± 85.8152)	198.570 (± 89.1780)	
Change From Baseline at Year 5 (n=20, 89, 22)	2.723 (± 52.1737)	-4.222 (± 48.2397)	-17.152 (± 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 (± 26.5862)	83.616 (± 25.6990)	107.818 (± 34.8418)	
Change From Baseline at Year 5 (n=21, 84, 21)	7.173 (± 15.9316)	-1.279 (± 20.0305)	-11.710 (± 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 (± 0.1616)	0.717 (± 0.1840)	0.593 (± 0.1802)	
Change From Baseline at Year 5 (n=20, 89, 22)	-0.066 (± 0.1344)	-0.061 (± 0.1320)	-0.037 (± 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 (± 7.4802)	-37.660 (± 35.2948)	-39.965 (± 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

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			

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			

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			

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			

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			

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

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

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			

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			

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

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

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

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

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

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

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

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

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

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