Clinical trial results:
APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP)

Summary

EudraCT number	2013-002987-17
Trial protocol	SE ES PT IT DE NL GB
Global end of trial date	17 August 2017

Results information

Result version number	v1 (current)
This version publication date	23 August 2018
First version publication date	23 August 2018

Trial information

Trial identification

Sponsor protocol code	ALN-TTR02-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01960348
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, MA, United States, 02142
Public contact	Investor Relations and Corporate Communications, Alnylam Pharmaceuticals, Inc., Investors@alnylam.com
Scientific contact	Chief Medical Officer , Alnylam Pharmaceuticals, Inc., medinfo@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	14 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2017
Global end of trial reached?	Yes
Global end of trial date	17 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of patisiran-LNP (ALN-TTR02) by evaluating the difference between the patisiran and placebo groups in the change from baseline of mNIS+7 score at 18 months

Protection of trial subjects:

An independent Data Monitoring Committee was implemented for the study and operated under a prespecified charter. The Data Monitoring Committee was responsible for monitoring the progress of the study and the safety of the participants

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Cyprus: 4
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 8

Worldwide total number of subjects	225
EEA total number of subjects	110

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)	130
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 225 patients with hATTR amyloidosis were enrolled and randomized in the study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Patisiran (ALN-TTR02)

Arm description:

All patients who received at least 1 dose of patisiran (ALN-TTR02)

Arm type	Experimental
Investigational medicinal product name	Patisiran
Investigational medicinal product code	ALN-TTR02
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients who were randomized into the active treatment group received 0.3 mg/kg patisiran (ALN-TTR02) every three weeks (q3w) administered as an approximately 80-minute IV infusion. In the event of a mild or moderate infusion related reaction (IRR), the infusion time may have been extended.

Arm title	Placebo

Arm description:

All patients who received at least 1 dose of placebo

Arm type	Placebo
Investigational medicinal product name	Normal saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients who were randomized into the control group received placebo (normal saline 0.9%) every three weeks (q3w) administered as an approximately 80-minute IV infusion. In the event of a mild or moderate infusion related reaction (IRR), the infusion time may have been extended.

Number of subjects in period 1	Patisiran (ALN-TTR02)	Placebo
Started	148	77
Completed	138	55
Not completed	10	22
Adverse event, not serious	2	2
Adverse event, serious fatal	6	5
Consent withdrawn by subject	1	11
Physician decision	-	1
Adverse event, serious non-fatal	-	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Patisiran (ALN-TTR02)
Reporting group description:	
All patients who received at least 1 dose of patisiran (ALN-TTR02)	
Reporting group title	Placebo
Reporting group description:	
All patients who received at least 1 dose of placebo	

Reporting group values	Patisiran (ALN-TTR02)	Placebo	Total
Number of subjects	148	77	225
Age categorical Units: Subjects			
Less than 65 years	86	44	130
65-74 years	53	24	77
Greater than or equal to 75 years	9	9	18
Age continuous Units: years			
arithmetic mean	59.6	62.2	
standard deviation	± 11.96	± 10.76	-
Gender categorical Units: Subjects			
Female	39	19	58
Male	109	58	167
Baseline NIS			
The Neuropathy Impairment Score is an assessment of motor weakness (NIS-W), sensation (NIS-S) and reflexes (NIS-R) scored based on physical exam findings.			
Units: Subjects			
<50	62	35	97
≥50	86	42	128
Genotype Class			
TTR genotype class, collected at baseline			
Units: Subjects			
Early onset V30M (<50 years of age at onset)	13	10	23
All other mutations (including late onset V30M)	135	67	202
Previous Tetramer Stabilizer Use			
Prior use of tafamidis, meglumine or diflunisal			
Units: Subjects			
Yes	78	41	119
No	70	36	106

End points

End points reporting groups

Reporting group title	Patisiran (ALN-TTR02)
Reporting group description:	
All patients who received at least 1 dose of patisiran (ALN-TTR02)	
Reporting group title	Placebo
Reporting group description:	
All patients who received at least 1 dose of placebo	
Subject analysis set title	Modified Intent-to-Treat (mITT) population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients who were randomized and received at least 1 dose of patisiran (ALN-TTR02) or placebo. Patients were analyzed according to the treatment to which they were randomized.	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All randomized patients who received at least 1 dose of patisiran (ALN-TTR02) or placebo, completed baseline and either the 9-month or 18-month mNIS+7 and Norfolk QoL-DN assessments, and did not experience any major protocol deviations that may impact the efficacy results. Patients were analyzed according to treatment received.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least 1 dose of patisiran (ALN-TTR02) or placebo. Patients were analyzed according to the treatment received.	
Subject analysis set title	Pharmacokinetic (PK) population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients in the Safety Population who provided at least 1 pharmacokinetic (PK) concentration measurement.	

Primary: Modified Neuropathy Impairment Score +7 (mNIS+7)

End point title	Modified Neuropathy Impairment Score +7 (mNIS+7)
End point description:	
The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in mNIS+7 at 18 months. The mNIS+7 is a composite score that quantitates motor, sensory, and autonomic neurologic impairment due to injury of large and small nerves.	
End point type	Primary
End point timeframe:	
18 months	

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	51		
Units: mNIS+7 points				
least squares mean (standard error)				
Change from Baseline in mNIS+7 at Month 18	-6.03 (± 1.739)	27.96 (± 2.602)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in mNIS+7. The model includes baseline mNIS+7 score as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [1]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-33.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.86
upper limit	-28.13
Variability estimate	Standard error of the mean
Dispersion value	2.974

Notes:

[1] - P=9.262E-24

Secondary: Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire

End point title	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in Norfolk QoL-DN at 18 months. The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that is sensitive to the different features of diabetic neuropathy - small fiber, large fiber, and autonomic nerve function.

End point type	Secondary

End point timeframe:

18 months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	48		
Units: Norfolk QOL-DN points				
least squares mean (standard error)				
Change from Baseline in Norfolk QoL-DN at Month 18	-6.7 (± 1.77)	14.4 (± 2.73)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in Norfolk QOL-DN total score. The model includes baseline Norfolk QOL-DN score as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline NIS, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [2]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.2
upper limit	-15
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[2] - P=1.103E-10

Secondary: Neurological Impairment Score-Weakness (NIS-W) score

End point title	Neurological Impairment Score-Weakness (NIS-W) score

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in NIS-W at 18 months. NIS-W is a measure of motor strength, comprised of cranial nerve and both upper and lower limb motor assessments.

End point type	Secondary

End point timeframe:

18 Months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	51		
Units: NIS-W points				
least squares mean (standard error)				
Change from Baseline in NIS-W at Month 18	0.05 (± 1.306)	17.93 (± 1.959)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in NIS-W. The model includes baseline NIS-W score as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [3]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-17.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.32
upper limit	-13.43
Variability estimate	Standard error of the mean
Dispersion value	2.254

Notes:

[3] - P=1.404E-13

Secondary: Rasch-built Overall Disability Scale (R-ODS) score

End point title	Rasch-built Overall Disability Scale (R-ODS) score

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in R-ODS score at 18 months. The R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations in patients.

End point type	Secondary

End point timeframe:

18 Months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	54		
Units: R-ODS points				
least squares mean (standard error)				
Change from Baseline in R-ODS at Month 18	0.0 (± 0.59)	-8.9 (± 0.88)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in R-ODS value. The model includes baseline R-ODS score as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline NIS, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [4]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	10.9
Variability estimate	Standard error of the mean
Dispersion value	1.01

Notes:

[4] - P=4.066E-16

Secondary: Timed 10-meter walk test (10-MWT, gait speed)

End point title	Timed 10-meter walk test (10-MWT, gait speed)

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in 10-MWT at 18 months. Ability to ambulate (gait speed) was assessed through the 10-meter walk test (10-MWT). The walk had to be completed without assistance from another person; ambulatory aids such as canes and walkers were permitted.

End point type	Secondary

End point timeframe:

18 Months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	55		
Units: m/sec				
least squares mean (standard error)				
Change from Baseline in 10-MWT at Month 18	0.077 (± 0.0242)	-0.235 (± 0.0358)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in 10-meter walk test result. The model includes baseline 10-meter walk test result as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline NIS, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [5]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	0.311
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.393
Variability estimate	Standard error of the mean
Dispersion value	0.0415

Notes:

[5] - P=1.875E-12

Secondary: Modified body mass index (mBMI)

End point title	Modified body mass index (mBMI)

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in mBMI at 18 months. The nutritional status of patients was evaluated using the mBMI; calculated as the product of BMI (weight in kilograms divided by the square of height in meters) and serum albumin (g/L).

End point type	Secondary

End point timeframe:

18 Months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	52		
Units: kg/m2 x albumin g/L				
least squares mean (standard error)				
Change from Baseline in mBMI at Month 18	-3.7 (± 9.57)	-119.4 (± 14.51)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in mBMI. The model includes baseline mBMI as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline NIS, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [6]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	115.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	82.4
upper limit	149
Variability estimate	Standard error of the mean
Dispersion value	16.91

Notes:

[6] - P=8.832E-11

Secondary: Autonomic symptoms questionnaire (Composite Autonomic Symptom Score [COMPASS 31])

End point title	Autonomic symptoms questionnaire (Composite Autonomic Symptom Score [COMPASS 31])

End point description:

The difference between the patisiran (ALN-TTR02) and placebo groups in the change from baseline in COMPASS 31 at 18 months. The COMPASS 31 is a measure of autonomic neuropathy symptoms. The questions evaluated 6 autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor).

End point type	Secondary

End point timeframe:

18 Months

End point values	Patisiran (ALN-TTR02)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	53		
Units: COMPASS 31 points				
least squares mean (standard error)				
Change from Baseline in COMPASS 31 at Month 18	-5.29 (± 1.300)	2.24 (± 1.940)		

Statistical analyses

Statistical analysis title	Placebo vs. Patisiran (ALN-TTR02)

Statistical analysis description:

In the mixed-effect model repeated measures (MMRM) model, the outcome variable is change from baseline in COMPASS-31 total score. The model includes baseline COMPASS-31 score as covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline NIS, genotype, age at hATTR symptom onset, previous tetramer stabilizer use and region.

Comparison groups	Patisiran (ALN-TTR02) v Placebo
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.89
upper limit	-3.16
Variability estimate	Standard error of the mean
Dispersion value	2.213

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred from the start of study drug administration through End of Study (Day 567), or Follow-up (Day 602) if the patient did not enter open-label extension study.

Adverse event reporting additional description:

AEs for patients with Rapid Disease Progression at Month 9 who stopped dosing were collected through Day 294 (42 days after last dose).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Patisiran (ALN-TTR02)

Reporting group description:

All patients who received at least 1 dose of patisiran (ALN-TTR02).

Reporting group title	Placebo

Reporting group description:

All patients who received at least 1 dose of placebo.

Serious adverse events	Patisiran (ALN-TTR02)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 148 (36.49%)	31 / 77 (40.26%)	
number of deaths (all causes)	7	6	
number of deaths resulting from adverse events	7	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Atypical fibroxanthoma			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colorectal cancer metastatic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal oncocytoma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 148 (1.35%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 148 (2.03%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Liver transplant			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device battery issue			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Amyloidosis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast mass			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 148 (0.68%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 148 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucinations, mixed			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Drug level increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint dislocation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary neuropathic amyloidosis			
subjects affected / exposed	0 / 148 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phimosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Syringomyelia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 148 (1.35%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	3 / 148 (2.03%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	2 / 148 (1.35%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 148 (1.35%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 148 (2.03%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure acute			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 148 (2.03%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	1 / 148 (0.68%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Restrictive cardiomyopathy			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dyssynchrony			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vertigo			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Maculopathy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous opacities			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 148 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 148 (5.41%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 148 (0.68%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 148 (0.68%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 148 (0.68%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis staphylococcal			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 148 (0.68%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 148 (2.03%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 148 (0.00%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urosepsis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	1 / 148 (0.68%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 148 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Patisiran (ALN-TTR02)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 148 (96.62%)	75 / 77 (97.40%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 148 (5.41%)	5 / 77 (6.49%)	
occurrences (all)	8	9	
Orthostatic hypotension			

subjects affected / exposed	7 / 148 (4.73%)	6 / 77 (7.79%)	
occurrences (all)	7	7	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	43 / 148 (29.05%)	17 / 77 (22.08%)	
occurrences (all)	68	35	
Fatigue			
subjects affected / exposed	18 / 148 (12.16%)	8 / 77 (10.39%)	
occurrences (all)	27	18	
Asthenia			
subjects affected / exposed	14 / 148 (9.46%)	8 / 77 (10.39%)	
occurrences (all)	25	11	
Pyrexia			
subjects affected / exposed	11 / 148 (7.43%)	5 / 77 (6.49%)	
occurrences (all)	12	6	
Peripheral swelling			
subjects affected / exposed	4 / 148 (2.70%)	4 / 77 (5.19%)	
occurrences (all)	6	6	
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	28 / 148 (18.92%)	7 / 77 (9.09%)	
occurrences (all)	145	79	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 148 (10.14%)	9 / 77 (11.69%)	
occurrences (all)	18	11	
Dyspnoea			
subjects affected / exposed	9 / 148 (6.08%)	0 / 77 (0.00%)	
occurrences (all)	13	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 148 (10.14%)	7 / 77 (9.09%)	
occurrences (all)	24	12	
Depression			
subjects affected / exposed	5 / 148 (3.38%)	5 / 77 (6.49%)	
occurrences (all)	5	7	

Investigations			
Weight decreased			
subjects affected / exposed	6 / 148 (4.05%)	7 / 77 (9.09%)	
occurrences (all)	6	7	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	25 / 148 (16.89%)	22 / 77 (28.57%)	
occurrences (all)	47	42	
Contusion			
subjects affected / exposed	4 / 148 (2.70%)	5 / 77 (6.49%)	
occurrences (all)	5	5	
Thermal burn			
subjects affected / exposed	4 / 148 (2.70%)	4 / 77 (5.19%)	
occurrences (all)	7	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	11 / 148 (7.43%)	5 / 77 (6.49%)	
occurrences (all)	12	6	
Supraventricular extrasystoles			
subjects affected / exposed	2 / 148 (1.35%)	5 / 77 (6.49%)	
occurrences (all)	2	6	
Atrioventricular block first degree			
subjects affected / exposed	0 / 148 (0.00%)	4 / 77 (5.19%)	
occurrences (all)	0	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 148 (12.84%)	11 / 77 (14.29%)	
occurrences (all)	24	37	
Headache			
subjects affected / exposed	16 / 148 (10.81%)	9 / 77 (11.69%)	
occurrences (all)	25	10	
Neuralgia			
subjects affected / exposed	10 / 148 (6.76%)	5 / 77 (6.49%)	
occurrences (all)	29	13	
Balance disorder			

subjects affected / exposed	8 / 148 (5.41%)	2 / 77 (2.60%)	
occurrences (all)	10	2	
Paraesthesia			
subjects affected / exposed	8 / 148 (5.41%)	3 / 77 (3.90%)	
occurrences (all)	23	5	
Somnolence			
subjects affected / exposed	5 / 148 (3.38%)	4 / 77 (5.19%)	
occurrences (all)	13	5	
Hypoaesthesia			
subjects affected / exposed	4 / 148 (2.70%)	5 / 77 (6.49%)	
occurrences (all)	6	5	
Syncope			
subjects affected / exposed	2 / 148 (1.35%)	8 / 77 (10.39%)	
occurrences (all)	2	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 148 (2.03%)	8 / 77 (10.39%)	
occurrences (all)	3	11	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 148 (5.41%)	1 / 77 (1.30%)	
occurrences (all)	11	1	
Eye disorders			
Cataract			
subjects affected / exposed	8 / 148 (5.41%)	5 / 77 (6.49%)	
occurrences (all)	10	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	50 / 148 (33.78%)	28 / 77 (36.36%)	
occurrences (all)	156	94	
Constipation			
subjects affected / exposed	22 / 148 (14.86%)	12 / 77 (15.58%)	
occurrences (all)	29	17	
Nausea			
subjects affected / exposed	22 / 148 (14.86%)	16 / 77 (20.78%)	
occurrences (all)	50	22	
Vomiting			

subjects affected / exposed	14 / 148 (9.46%)	6 / 77 (7.79%)	
occurrences (all)	20	27	
Dyspepsia			
subjects affected / exposed	12 / 148 (8.11%)	3 / 77 (3.90%)	
occurrences (all)	23	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 148 (5.41%)	5 / 77 (6.49%)	
occurrences (all)	8	5	
Abdominal pain upper			
subjects affected / exposed	3 / 148 (2.03%)	6 / 77 (7.79%)	
occurrences (all)	3	8	
Haemorrhoids			
subjects affected / exposed	1 / 148 (0.68%)	5 / 77 (6.49%)	
occurrences (all)	3	7	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	10 / 148 (6.76%)	2 / 77 (2.60%)	
occurrences (all)	51	2	
Skin ulcer			
subjects affected / exposed	5 / 148 (3.38%)	5 / 77 (6.49%)	
occurrences (all)	7	6	
Skin lesion			
subjects affected / exposed	2 / 148 (1.35%)	4 / 77 (5.19%)	
occurrences (all)	2	4	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	6 / 148 (4.05%)	7 / 77 (9.09%)	
occurrences (all)	9	12	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	12 / 148 (8.11%)	1 / 77 (1.30%)	
occurrences (all)	18	1	
Arthralgia			
subjects affected / exposed	11 / 148 (7.43%)	0 / 77 (0.00%)	
occurrences (all)	13	0	
Back pain			

subjects affected / exposed	10 / 148 (6.76%)	6 / 77 (7.79%)	
occurrences (all)	11	9	
Pain in extremity			
subjects affected / exposed	10 / 148 (6.76%)	8 / 77 (10.39%)	
occurrences (all)	13	12	
Osteoporosis			
subjects affected / exposed	7 / 148 (4.73%)	7 / 77 (9.09%)	
occurrences (all)	7	7	
Muscular weakness			
subjects affected / exposed	5 / 148 (3.38%)	11 / 77 (14.29%)	
occurrences (all)	8	17	
Myalgia			
subjects affected / exposed	2 / 148 (1.35%)	4 / 77 (5.19%)	
occurrences (all)	4	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	19 / 148 (12.84%)	12 / 77 (15.58%)	
occurrences (all)	40	18	
Nasopharyngitis			
subjects affected / exposed	15 / 148 (10.14%)	6 / 77 (7.79%)	
occurrences (all)	26	11	
Upper respiratory tract infection			
subjects affected / exposed	13 / 148 (8.78%)	5 / 77 (6.49%)	
occurrences (all)	16	6	
Influenza			
subjects affected / exposed	11 / 148 (7.43%)	4 / 77 (5.19%)	
occurrences (all)	13	4	
Bronchitis			
subjects affected / exposed	9 / 148 (6.08%)	2 / 77 (2.60%)	
occurrences (all)	11	2	
Gastroenteritis			
subjects affected / exposed	4 / 148 (2.70%)	4 / 77 (5.19%)	
occurrences (all)	5	4	
Metabolism and nutrition disorders			
Vitamin D deficiency			

subjects affected / exposed	7 / 148 (4.73%)	4 / 77 (5.19%)	
occurrences (all)	7	4	
Decreased appetite			
subjects affected / exposed	6 / 148 (4.05%)	5 / 77 (6.49%)	
occurrences (all)	6	9	
Dehydration			
subjects affected / exposed	1 / 148 (0.68%)	5 / 77 (6.49%)	
occurrences (all)	1	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	Reordered secondary endpoints and modified methods of analysis Modified Inclusion Criterion #7 to allow an INR of ≤3 only for patients on warfarin Clarified definition of "highly effective birth control" Modified the premedication regimen to be administered the night prior to study drug administration and on the day of study drug administration
21 March 2014	Clarified that entry criteria, besides Inclusion Criteria #3 and #4, would continue to be assessed at both the Screening and the Screening/ Baseline visits Modified Inclusion Criterion #1 to allow for enrollment of subjects up to 85 years of age (inclusive) Modified Inclusion Criterion #3: the lower limit of the NIS changed from 10 to 5 Modified Inclusion Criterion #4 to include patients with a NCS sum of the sural sensory nerve action potential, the tibial compound muscle action potential and the peroneal CMAP ≥2 Modified Inclusion Criterion #6: platelet count changed from ≥100,000 cells/mm3 to ≥50000 cells/mm3 Modified Inclusion Criterion #7: INR value changed from ≤3 to ≤3.5 Clarified Exclusion Criterion #1 to exclude patients with vitamin A levels consistent with vitamin A deficiency Removed Exclusion Criterion #18 (removed: Participated in a clinical study with an antisense oligonucleotide for more than 3 months; if in a clinical study with antisense oligonucleotide for ≤3 months, must have completed a 3-month wash-out prior to start of study drug administration in this study) Removed Diflunisal from Exclusion Criterion #19 and added to Exclusion Criterion #20 to clarify that a 3-day washout period prior to start of study drug for this particular agent
24 April 2014	Expanded the screening window from 28 days to 42 days to accommodate traveling patients
04 August 2014	Modified Inclusion Criterion #3: the upper limit NIS changed from 100 to 130, and the requirement for having a PND score of ≤3b was added Modified Inclusion Criterion #7 to remove albumin criterion and to increase INR criterion from ≤1.2 to ≤2.0 Modified Inclusion Criterion #8: serum creatinine changed from ≤1.5 to ≤2 × ULN Modified Inclusion Criterion #9 to exclude only patients with an active hepatitis B or hepatitis C infection Modified Inclusion Criterion #1 to change period from 1 month to 75 days after last dose of study drug for women of child-bearing potential Modified Inclusion Criterion #11 to extend the period that males with partners of child-bearing potential must use 1 barrier method and 1 additional method of contraception from 1 month to 75 days after the last dose of study drug Removed Exclusion Criterion #1 (has vitamin A level consistent with vitamin A deficiency) Clarified Exclusion Criterion #16 to state that patients with a history of alcohol abuse within the past 2 years or daily heavy alcohol consumption Modified Exclusion Criterion #17 to exclude patients who participated in a clinical study with antisense oligonucleotide unless there is a 3- month wash-out period Modified Exclusion Criterion #24 to define "under legal protection"

08 September 2015	Implemented a reduced dose of dexamethasone for the protocol-specified premedication regimen on the day of study drug administration, and removed administration of premedication the night before study drug administration. Specified that patients who are intolerant of 10 mg IV dexamethasone or equivalent on the day of infusion may be considered for further stepwise reduction in dexamethasone or equivalent after consultation with the Medical Monitor Updated the risk benefit assessment to reflect liver function test abnormalities and risk for osteoporosis Modified Inclusion Criterion #4: added ulnar SNAP and ulnar CMAP measurements to the qualifying NCS Modified Inclusion Criterion #7: permitted enrollment of patients with a total bilirubin level elevation to ≤2 x upper limit of normal Modified Exclusion Criterion #14: clarified that patients with any uncontrolled cardiac arrhythmia or unstable angina are not permitted to enroll in the study Included the option for patients to permanently discontinue study treatment and remain on study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported