



Clinical trial results:

A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of ALN-TTR02 in Patients With Familial Amyloidotic Polyneuropathy Who Have Previously Received ALN-TTR02

Summary

EudraCT number	2013-001644-65
Trial protocol	PT SE ES
Global end of trial date	31 August 2016

Results information

Result version number	v1 (current)
This version publication date	14 September 2017
First version publication date	14 September 2017

Trial information

Trial identification

Sponsor protocol code	ALN-TTR02-003
-----------------------	---------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01961921
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., Alnylam Pharmaceuticals, Inc., 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	24 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2016
Global end of trial reached?	Yes
Global end of trial date	31 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety of long-term dosing with patisiran.

Protection of trial subjects:

The safety assessments included the incidence and severity of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry and urinalysis), electrocardiogram (ECG), vital signs and physical examinations which were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2013
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	Portugal: 8
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	27
EEA total number of subjects	25

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)	14
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 27 subjects who met entry criteria were enrolled.

Pre-assignment period milestones

Number of subjects started	27
Number of subjects completed	27

Period 1

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

Arms

Arm title	All Patients
-----------	--------------

Arm description:

Patients received 0.3 mg/kg of ALN-TTR02 (patisiran) every three weeks.

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

Dosage and administration details:

0.3 mg/kg of ALN-TTR02 (patisiran) every three weeks

Number of subjects in period 1	All Patients
Started	27
Completed	25
Not completed	2
Adverse event, serious fatal	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
-----------------------	---------------

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	27	27	
Age categorical			
All patients who received at least one dose of ALN-TTR02 (patisiran)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	57.9		
standard deviation	± 15.36	-	
Gender categorical			
All patients who received at least one dose of ALN-TTR02 (patisiran)			
Units: Subjects			
Female	9	9	
Male	18	18	
FAP Stage			
All patients who received at least one dose of ALN-TTR02 (patisiran)			
Units: Subjects			
FAP Stage I: Unimpaired ambulation	24	24	
FAP Stage II: Assistance with ambulation required	3	3	
FAP Stage III: Wheelchair-bound or bedridden	0	0	

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description: Patients received 0.3 mg/kg of ALN-TTR02 (patisiran) every three weeks.	

Primary: Safety of long-term dosing with ALN-TTR02 (patisiran) in hATTR patients

End point title	Safety of long-term dosing with ALN-TTR02 (patisiran) in hATTR patients ^[1]
-----------------	--

End point description:

The proportion of subjects experiencing adverse events (AEs), serious adverse events (SAEs) and study drug discontinuation

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

End point timeframe:

Up to 56 days post last dose

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: No inferential analyses were conducted as the primary endpoint was safety and tolerability. Analyses were descriptive in nature.

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Number of subjects				
At least 1 TEAE	26			
At least 1 SAE	7			
Study Discontinuation for any reason	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum TTR Levels

End point title	Serum TTR Levels
-----------------	------------------

End point description:

TTR levels, measured using the ELISA method

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

End point timeframe:

Up to 56 days post last dose

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: TTR Reduction %				
arithmetic mean (standard deviation)				
Individual Mean TTR (%) Reduction from Baseline ov	82.06 (± 1.33)			
Individual Mean Predose TTR (%) Reduction from Bas	79.73 (± 1.45)			
Individual Maximum TTR (%) Reduction from Baseline	92.54 (± 0.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neurologic impairment

End point title	Neurologic impairment
End point description:	The mNIS+7 assessment is a composite measure of neurologic impairment that provides a comprehensive measure of large and small fiber function that encompasses the totality of the motor, sensory, and autonomic deficits seen in hATTR amyloidosis patients with polyneuropathy. An increase from baseline in mNIS+7 score suggests worsening of neurological impairment, and a decrease from baseline suggests improvement.
End point type	Secondary
End point timeframe:	Up to 24 months

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: mNIS+7				
arithmetic mean (standard deviation)				
mNIS+7 score (Baseline)	53.02 (± 35.63)			
mNIS+7 (Change from baseline at 24 months)	-6.95 (± 2.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life and disability

End point title	Quality of life and disability
End point description:	Quality of life (EQ-5D and EQ-VAS) and disability (R-ODS). The overall EQ-5D is measured on a scale

from 0 to 1, with 0 being worst and 1 best. The EQ-VAS is measured on a scale of 0-100, with 0 being the worst and 100 the best.

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

End point timeframe:

Up to 24 months

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Score				
arithmetic mean (standard deviation)				
EQ-5D (Baseline)	0.78 (± 0.14)			
EQ-5D (Score change from baseline to 24 months)	-0.01 (± 0.02)			
EQ-VAS (Baseline)	67.9 (± 17.85)			
EQ-VAS (Score change from baseline to 24 months)	1.7 (± 2.53)			
R-ODS (Baseline)	38.1 (± 8.61)			
R-ODS (Score change from baseline to 24 months)	-1.8 (± 0.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Motor function

End point title	Motor function
-----------------	----------------

End point description:

Timed 10-meter walk test and test of grip strength

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

End point timeframe:

Up to 24 months

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: m/sec or kg				
arithmetic mean (standard deviation)				
10-meter Walk Test at Baseline (m/sec)	1.14 (± 0.79)			
10-meter Walk Test Change from baseline at 24 mont	0.03 (± 0.04)			
Hand Grip Strength at Baseline (kg)	25.81 (± 11.86)			
Hand Grip Strength Change from baseline at 24 mont	1.49 (± 1.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Nutritional status (modified body mass index, mBMI)

End point title	Nutritional status (modified body mass index, mBMI)
-----------------	---

End point description:

Nutritional status of patients will be evaluated using the mBMI, calculated as BMI (kg/m²) multiplied by albumin (g/L). An increase from baseline in mBMI suggests improvement, and a decrease from baseline suggests worsening

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

End point timeframe:

Up to 24 months

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: kg/m ² x albumin g/L				
arithmetic mean (standard deviation)				
kg/m ² x albumin g/L (Baseline)	1030.49 (± 168.64)			
Kg/m ² x albumin g/L (Change from baseline at 24 mo)	-60.76 (± 34.86)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigators reported all AEs that occurred after the start of study drug administration on Day 0 (Baseline) through 21 or 56 days after the last dose of study drug administration (depending on enrollment into the open-label global extension study).

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Safety Population
-----------------------	-------------------

Reporting group description:

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

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac amyloidosis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders Acute prerenal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 27 (3.70%) 0 / 1 0 / 0		
Musculoskeletal and connective tissue disorders Osteonecrosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 27 (7.41%) 0 / 2 0 / 0		
Infections and infestations Abscess limb subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 27 (3.70%) 0 / 1 0 / 0		
Osteomyelitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 27 (3.70%) 0 / 1 0 / 0		
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 27 (3.70%) 0 / 1 0 / 0		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 27 (3.70%) 0 / 1 0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events subjects affected / exposed	26 / 27 (96.30%)		

Vascular disorders			
Flushing			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	93		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Infusion site extravasation			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	8		
Early satiety			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gait disturbance			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Infusion site erythema			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	46		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 30		
Depression subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Investigations Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Weight decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Injury, poisoning and procedural complications Wound subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 10		
Ankle fracture subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Fall subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Foot fracture subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4		
Ligament rupture subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Nervous system disorders Neuralgia subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5		

Headache subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Hypoaesthesia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4		
Visual field defect subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4		
Eye disorders Cataract subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Macular degeneration subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Macular fibrosis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Visual acuity reduced subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 6		
Vomiting subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 8		
Nausea subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 6		
Abdominal pain			

<p>subjects affected / exposed occurrences (all)</p> <p>Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Dyspepsia subjects affected / exposed occurrences (all)</p>	<p>2 / 27 (7.41%) 2</p> <p>1 / 27 (3.70%) 2</p> <p>2 / 27 (7.41%) 4</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Erythema subjects affected / exposed occurrences (all)</p> <p>Skin ulcer subjects affected / exposed occurrences (all)</p>	<p>2 / 27 (7.41%) 2</p> <p>2 / 27 (7.41%) 3</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Musculoskeletal pain subjects affected / exposed occurrences (all)</p> <p>Osteoporosis subjects affected / exposed occurrences (all)</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Osteoarthritis subjects affected / exposed occurrences (all)</p> <p>Osteonecrosis subjects affected / exposed occurrences (all)</p> <p>Osteopenia</p>	<p>3 / 27 (11.11%) 3</p> <p>3 / 27 (11.11%) 3</p> <p>2 / 27 (7.41%) 3</p> <p>2 / 27 (7.41%) 2</p> <p>2 / 27 (7.41%) 2</p> <p>2 / 27 (7.41%) 2</p>		

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 8		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 8		
Bronchitis subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 7		
Cellulitis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Influenza subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Osteomyelitis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Sinusitis subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Wound infection subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2015	Protocol Amendment 1.0 Implemented a reduced dose of dexamethasone premedication as part of the protocol-specified premedication regimen

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported