Clinical trial results:
A Phase 2, Open-Label, Multi-Dose, Dose Escalation Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous Infusions of ALN-TTR02 (patisiran) in Patients with TTR Amyloidosis.

Summary

EudraCT number	2012-000467-24
Trial protocol	SE PT DE ES
Global end of trial date	27 January 2014

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ALN-TTR02-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617967
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 & Corporate Communication, Alnylam Pharmaceuticals, Inc., investors@alnylam.com
Scientific contact	Senior Vice President, Clinical Development, 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	07 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2014
Global end of trial reached?	Yes
Global end of trial date	27 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the safety and tolerability of multiple doses of ALN-TTR02 (patisiran).

Protection of trial subjects:

A Safety Review Committee (SRC) was in place for this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2012
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	Spain: 3
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	Brazil: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Portugal: 9
Worldwide total number of subjects	29
EEA total number of subjects	27

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)	17

From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 29 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1

Arm description:

Patients received 0.010 mg/kg of ALN-TTR02 (patisiran) every four 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:

0.010 mg/kg of ALN-TTR02 (patisiran) every four weeks

Arm title	Cohort 2

Arm description:

Patients received 0.050 mg/kg of ALN-TTR02 (patisiran) every four 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:

0.050 mg/kg of ALN-TTR02 (patisiran) every four weeks

Arm title	Cohort 3

Arm description:

Patients received 0.150 mg/kg of ALN-TTR02 (patisiran) every four weeks

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

Dosage and administration details:

0.150 mg/kg of ALN-TTR02 (patisiran) every four weeks

Arm title	Cohort 4 and 5

Arm description:

Patients received 0.30 mg/kg of ALN-TTR02 (patisiran) every four 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:

0.30 mg/kg of ALN-TTR02 (patisiran) every four weeks

Arm title	Cohort 6

Arm description:

Patients received 0.30 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:

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

Arm title	Cohort 7, 8, and 9

Arm description:

Patients received 0.30 mg/kg of ALN-TTR02 (patisiran) every three weeks with alternative premedication regimen

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:

0.30 mg/kg of ALN-TTR02 (patisiran) every three weeks with alternative premedication regimen

Arm title	Cohort 6, 7, 8 and 9

Arm description:

PK results for Cohorts 6, 7, 8 and 9 have been grouped together.

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:

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

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	4	3	3
Completed	3	3	3
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Cohort 4 and 5	Cohort 6	Cohort 7, 8, and 9
Started	7	3	9
Completed	7	3	8
Not completed	0	0	1
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	Cohort 6, 7, 8 and 9
Started	12
Completed	11
Not completed	1
Consent withdrawn by subject	-
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	29	29	
Age categorical 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)	17	17	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55.6		
standard deviation	± 15.61	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	20	20	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Patients received 0.010 mg/kg of ALN-TTR02 (patisiran) every four weeks	
Reporting group title	Cohort 2
Reporting group description:	
Patients received 0.050 mg/kg of ALN-TTR02 (patisiran) every four weeks	
Reporting group title	Cohort 3
Reporting group description:	
Patients received 0.150 mg/kg of ALN-TTR02 (patisiran) every four weeks	
Reporting group title	Cohort 4 and 5
Reporting group description:	
Patients received 0.30 mg/kg of ALN-TTR02 (patisiran) every four weeks	
Reporting group title	Cohort 6
Reporting group description:	
Patients received 0.30 mg/kg of ALN-TTR02 (patisiran) every three weeks	
Reporting group title	Cohort 7, 8, and 9
Reporting group description:	
Patients received 0.30 mg/kg of ALN-TTR02 (patisiran) every three weeks with alternative premedication regimen	
Reporting group title	Cohort 6, 7, 8 and 9
Reporting group description:	
PK results for Cohorts 6, 7, 8 and 9 have been grouped together.	

Primary: Safety and tolerability in ATTR patients

End point title	Safety and tolerability in ATTR patients[1][2]
End point description:	
The number of subjects experiencing adverse events (AEs), serious adverse events (SAEs) and study drug discontinuation (due to any reason).	
End point type	Primary
End point timeframe:	
Up to 56 days post first 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.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics have been reported for all cohorts in the baseline period. Patients in the arm titled 'Cohort 6' and the arm titled 'Cohort 7, 8 and 9' received 300 µg/kg ALN-TTR02 (patisiran) every 3 weeks. Therefore these two arms have been combined in the statistical analysis of PK parameters and are reported as 'Cohort 6, 7, 8 and 9'. The arms have not been combined for reporting of other endpoints due to the use of different premedication regimens.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4 and 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	7
Units: subjects				
At least 1 Treatment Emergent Adverse Event	1	3	1	7
At least 1 Serious TEAE	0	0	0	1
Study Drug Discontinuation For Any Reason	1	0	0	0

End point values	Cohort 6	Cohort 7, 8, and 9		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: subjects				
At least 1 Treatment Emergent Adverse Event	3	7		
At least 1 Serious TEAE	0	1		
Study Drug Discontinuation For Any Reason	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTR02 (patisiran) - Cmax

End point title	Pharmacokinetic parameters of ALN-TTR02 (patisiran) -

End point description:

Cmax of ALN-TTR02 (patisiran)

End point type	Secondary

End point timeframe:

Up to 208 days post first dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics have been reported for all cohorts in the baseline period. Patients in the arm titled 'Cohort 6' and the arm titled 'Cohort 7, 8 and 9' received 300 µg/kg ALN-TTR02 (patisiran) every 3 weeks. Therefore these two arms have been combined in the statistical analysis of PK parameters and are reported as 'Cohort 6, 7, 8 and 9'. The arms have not been combined for reporting of other endpoints due to the use of different premedication regimens.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4 and 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[4]	3	3	7[5]
Units: ng/ml				
arithmetic mean (standard deviation)				
Cmax - Day 0	145 (± 23)	672 (± 473)	2560 (± 295)	6053 (± 1326)

Cmax - Day 21 or 28	106 (± 37)	683 (± 391)	3243 (± 986)	3782 (± 1259)

Notes:

[4] - N=3 at Day 28 due to 1 subject not completing study

[5] - N = 6 at Day 28 as 1 subject excluded from the calculation of descriptive statistics

End point values	Cohort 6, 7, 8 and 9			
Subject group type	Reporting group			
Number of subjects analysed	12[6]			
Units: ng/ml				
arithmetic mean (standard deviation)				
Cmax - Day 0	4539 (± 1362)			
Cmax - Day 21 or 28	3314 (± 1253)			

Notes:

[6] - N=11 at Day 21 due to 1 subject not completing study

Statistical analyses

No statistical analyses for this end point

Secondary: Serum transythretin (TTR) protein

End point title	Serum transythretin (TTR) protein[7]

End point description:

Percent lowering of TTR relative to pretreatment/baseline levels

End point type	Secondary

End point timeframe:

Up to 208 days post first dose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics have been reported for all cohorts in the baseline period. Patients in the arm titled 'Cohort 6' and the arm titled 'Cohort 7, 8 and 9' received 300 µg/kg ALN-TTR02 (patisiran) every 3 weeks. Therefore these two arms have been combined in the statistical analysis of PK parameters and are reported as 'Cohort 6, 7, 8 and 9'. The arms have not been combined for reporting of other endpoints due to the use of different premedication regimens.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4 and 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	7
Units: percent				
arithmetic mean (standard deviation)				
Mean Percent TTR Reduction at Day 21 or 28	-8.9 (± 9.91)	-21.7 (± 1.69)	-51.6 (± 22.84)	-73.9 (± 8.41)
Mean Percent TTR Reduction at Day 42 or 56	-20.3 (± 20.27)	-14.6 (± 15.8)	-44.7 (± 12.11)	-62.8 (± 25.11)

End point values	Cohort 6	Cohort 7, 8, and 9		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		

Units: percent				
arithmetic mean (standard deviation)				
Mean Percent TTR Reduction at Day 21 or 28	-78 (± 7.55)	-80.7 (± 10.14)		
Mean Percent TTR Reduction at Day 42 or 56	-78.7 (± 9.77)	-73.3 (± 19.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTR02 (patisiran) - AUC

End point title	Pharmacokinetic parameters of ALN-TTR02 (patisiran) - AUC[8]

End point description:

AUC of ALN-TTR02 (patisiran)

End point type	Secondary

End point timeframe:

Up to 208 days post first dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics have been reported for all cohorts in the baseline period. Patients in the arm titled 'Cohort 6' and the arm titled 'Cohort 7, 8 and 9' received 300 µg/kg ALN-TTR02 (patisiran) every 3 weeks. Therefore these two arms have been combined in the statistical analysis of PK parameters and are reported as 'Cohort 6, 7, 8 and 9'. The arms have not been combined for reporting of other endpoints due to the use of different premedication regimens.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4 and 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[9]	3	3	7[10]
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AUC 0-last : Day 0	2738 (± 3159)	9604 (± 10588)	18998 (± 5066)	53724 (± 35814)
AUC 0-last : Day 21 or Day 28	2799 (± 2645)	4884 (± 4652)	27748 (± 17081)	30013 (± 15935)

Notes:

[9] - N=3 at Day 28 due to 1 subject not completing study

[10] - N = 6 at Day 28 as 1 subject excluded from the calculation of descriptive statistics

End point values	Cohort 6, 7, 8 and 9			
Subject group type	Reporting group			
Number of subjects analysed	12[11]			
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AUC 0-last : Day 0	39741 (± 33373)			
AUC 0-last : Day 21 or Day 28	25958 (± 28460)			

Notes:
[11] - N=11 at Day 21 due to 1 subject not completing study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Investigator reported all AEs observed or reported after the first dose of study drug and through Day 56, regardless of their relationship to study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

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	2 / 29 (6.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis	Additional description: Right arm cellulitis due to extravasation		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
sepsis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	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	23 / 29 (79.31%)		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Asthenia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	6		
Vessel puncture site haematoma			
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	23		
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Gastrointestinal disorders			

Vomiting subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3 2 / 29 (6.90%) 2 2 / 29 (6.90%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2 4 / 29 (13.79%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2012	Protocol Amendment 1.0 • Removed the requirement that the SRC review safety data on all patients within a dose level between the first and second doses of study drug based on favourable single-dose safety data that emerged from the completed Phase 1 studies of ALN-TTR02 (patisiran) at doses greater than or equal to the proposed highest dose in this study. • Extended the postdose on-site observation period from 6 hours to 24 hours post infusion.
16 January 2013	Protocol Amendment 2.0 • Added alternative dosing regimens

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 June 2012	Sponsor notified agencies of a potential safety event in nonclinical toxicology study. Study continued based on human safety and tolerability data from Phase 1 study with ALN-TTR02 (patisiran) and data from other LNP (lipid nanoparticle) based programs.	26 July 2012

Notes:

Limitations and caveats

None reported