Clinical trial results:
A Phase 2, Open-Label Trial to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics and Exploratory Clinical Activity of ALN-TTRSC in Patients with Transthyretin (TTR) Cardiac Amyloidosis

Summary

EudraCT number	2013-002856-33
Trial protocol	GB
Global end of trial date	05 January 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	ALN-TTRSC-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01981837
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	09 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 January 2015
Global end of trial reached?	Yes
Global end of trial date	05 January 2015
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-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis.

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	06 January 2014
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	United Kingdom: 10
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	26
EEA total number of subjects	10

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)	7
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 26 patients 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?	Yes
Arm title	ALN-TTRSC (revusiran) 5.0 mg/kg

Arm description:

Patients received 5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses

Arm type	Experimental
Investigational medicinal product name	Revusiran
Investigational medicinal product code	ALN-TTRSC
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses. Patients received a daily dose of ALN-TTRSC (revusiran) over 5 consecutive days (Days 0, 1, 2, 3, and 4) and then they received once weekly doses of ALN-TTRSC (revusiran) for 5 weeks (Days 7, 14, 21, 28, and 35).

Arm title	ALN-TTRSC (revusiran) 7.5 mg/kg

Arm description:

Patients received 7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses

Arm type	Experimental
Investigational medicinal product name	Revusiran
Investigational medicinal product code	ALN-TTRSC
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses. Patients received a daily dose of ALN-TTRSC (revusiran) over 5 consecutive days (Days 0, 1, 2, 3, and 4) and then they received once weekly doses of ALN-TTRSC (revusiran) for 5 weeks (Days 7, 14, 21, 28, and 35).

Number of subjects in period 1	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg
Started	23	3
Completed	23	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	26	26	
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)	7	7	
From 65-84 years	19	19	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	68.1		
standard deviation	± 6.36	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	23	23	

End points

End points reporting groups

Reporting group title	ALN-TTRSC (revusiran) 5.0 mg/kg
Reporting group description:	
Patients received 5.0 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses	
Reporting group title	ALN-TTRSC (revusiran) 7.5 mg/kg
Reporting group description:	
Patients received 7.5 mg/kg of ALN-TTRSC (revusiran) for a total of 10 doses	

Primary: Safety and tolerability of multiple doses of ALN-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis

End point title	Safety and tolerability of multiple doses of ALN-TTRSC (revusiran) in patients with ATTR cardiac amyloidosis[1]
End point description:	
The number of patients 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 90 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.

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: patients				
At least 1 Treatment Emergent Adverse Event (TEAE)	17	3		
At least 1 Serious TEAE	3	0		
Study Drug Discontinuation For Any Reason	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): AUC

End point title	Pharmacokinetic parameters of ALN-TTRSC (revusiran): AUC
End point description:	
Partial area under the plasma concentration-time curve from time 0 to 24 hours (AUC 0-24) and area under the curve from time 0 to the last quantifiable concentration (AUC 0-last) of ALN-TTRSC (revusiran)	
End point type	Secondary

End point timeframe:

Up to 90 days post first dose

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AUC 0-24: Day 0	9523.2 (± 3606.45)	16006.2 (± 1728)		
AUC 0-last: Day 0	9217.2 (± 3746.44)	12684.8 (± 6546.56)		
AUC 0-24: Day 4	13364.4 (± 6241.06)	29124 (± 6241.55)		
AUC 0-last: Day 4	4310.2 (± 1425.93)	7547.5 (± 1186.01)		
AUC 0-24: Day 35	9960.7 (± 5554.52)	27122.5 (± 3826.16)		
AUC 0-last: Day 35	7853.3 (± 6398.12)	6102.6 (± 989.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum transthyretin (TTR) protein

End point title	Serum transthyretin (TTR) protein

End point description:

Percent lowering of TTR relative to pretreatment/baseline levels

End point type	Secondary

End point timeframe:

Up to 90 days post first dose

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: percent				
arithmetic mean (standard deviation)				
Mean Percent Change of Serum TTR at Day 21	-80.208 (± 11.2259)	-91.431 (± 4.2603)		
Mean Percent Change of Serum TTR at Day 42	-83.593 (± 10.9567)	-90.232 (± 5.7909)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): Cmax

End point title	Pharmacokinetic parameters of ALN-TTRSC (revusiran): Cmax
End point description:	
Maximum observed plasma concentration (Cmax) of ALN-TTRSC (revusiran)	
End point type	Secondary
End point timeframe:	
Up to 90 days post first dose	

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax: Day 0	814.5 (± 574.57)	1043 (± 71.842)		
Cmax: Day 4	942.9 (± 322.33)	1503 (± 205.99)		
Cmax: Day 35	691 (± 394.14)	1263 (± 156.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): tmax

End point title	Pharmacokinetic parameters of ALN-TTRSC (revusiran): tmax
End point description:	
Time of maximum observed plasma concentration (tmax) of ALN-TTRSC (revusiran)	
End point type	Secondary
End point timeframe:	
Up to 90 days	

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: hours				
arithmetic mean (standard deviation)				
tmax: Day 0	4.11 (± 2.1618)	5.3 (± 1.0833)		
tmax: Day 4	2.292 (± 1.8866)	3.317 (± 2.3238)		
tmax: Day 35	2.879 (± 2.2485)	5.272 (± 1.0301)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of ALN-TTRSC (revusiran): CLss/F

End point title	Pharmacokinetic parameters of ALN-TTRSC (revusiran): CLss/F

End point description:

Systemic clearance (CLss/F) of ALN-TTRSC (revusiran)

End point type	Secondary

End point timeframe:

Up to 90 days post first dose

End point values	ALN-TTRSC (revusiran) 5.0 mg/kg	ALN-TTRSC (revusiran) 7.5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	3		
Units: L/h/kg				
arithmetic mean (standard deviation)				
CLss/F: Day 4	0.5034 (± 0.34314)	0.2667 (± 0.064487)		
CLss/F: Day 35	0.2602 (± 0.16303)	0.07163 (± 0.009483)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Investigator reported all AEs that occurred after the first dose of study drug through the Day 63 or Early Termination visit regardless of their relationship to study drug or clinical significance.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 26 (3.85%)		
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	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 26 (76.92%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Injection site erythema			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	6		
Injection site bruising			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Injection site rash			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4 2 / 26 (7.69%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 8 3 / 26 (11.54%) 4 2 / 26 (7.69%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2013	Protocol Amendment 1 • The method of acceptable contraception for study participants was revised to reflect MHRA guidelines
16 October 2013	Protocol Amendment 2 • Increased patient numbers from 12 to 15 • Study drug dose decreased from 7.5 mg/kg to 5.0 mg/kg
21 January 2014	Protocol Amendment 3 • Changes to timings of pharmacokinetic blood draws • Measurement of vitamin A serum levels added to the Schedule of Assessments for the Day 35 visit
20 May 2014	Protocol Amendment 4 • The number of patients was increased to approximately 25 patients • Inclusion Criterion #2 was changed to include only cardiac amyloidosis patients with a TTR mutation • Exclusion Criterion #5 was modified to exclude patients with vitamin A levels consistent with vitamin A deficiency (ie, <20 µg/dL)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported