



Clinical trial results:

An Open-Label Study To Evaluate The Efficacy And Safety Of Revusiran In Patients With Transthyretin-Mediated Familial Amyloidotic Polyneuropathy With Disease Progression Post Orthotopic Liver Transplant

Summary

EudraCT number	2015-002603-29
Trial protocol	SE PT ES GB
Global end of trial date	06 February 2017

Results information

Result version number	v1 (current)
This version publication date	21 February 2018
First version publication date	21 February 2018

Trial information

Trial identification

Sponsor protocol code	ALN-TTRSC-005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02595983
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, United States, 02142
Public contact	Investor Relations and Corporate Communications, Alnylam Pharmaceuticals Inc, Investors@alnylam.com
Scientific contact	Chief Medical Officer, 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	02 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2017
Global end of trial reached?	Yes
Global end of trial date	06 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the efficacy of revusiran in patients with transthyretin (TTR)-amyloidosis (hATTR amyloidosis) with polyneuropathy, with disease progression post-orthotopic liver transplant (OLT) by evaluating the reduction in serum TTR level compared to baseline.

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	28 December 2015
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	Portugal: 3
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	10
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 12 patients with hATTR amyloidosis with polyneuropathy who had neuropathy progression following OLT were enrolled and treated in this study.

Pre-assignment period milestones

Number of subjects started	12
Number of subjects completed	12

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
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Arm description:

All patients who received at least 1 dose of the study drug

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:

Patients received 5 daily doses of 500 mg revusiran (Days 0 through 4) and a dose of 500 mg on Day 7, followed by once weekly 500 mg doses for the duration of the study, until termination of dosing

Number of subjects in period 1	All Patients
Started	12
Completed	8
Not completed	4
Adverse event, serious fatal	2
Consent withdrawn by subject	1
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	12	12	
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)	10	10	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	55.8		
standard deviation	± 8.65	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	9	9	

Subject analysis sets

Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least a single dose of study drug.	

Reporting group values	Safety		
Number of subjects	12		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	10		

From 65-84 years	2		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean	55.8		
standard deviation	± 8.65		
Gender categorical			
Units: Subjects			
Female	3		
Male	9		

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description: All patients who received at least 1 dose of the study drug	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least a single dose of study drug.	

Primary: Serum TTR over 6 months

End point title	Serum TTR over 6 months ^[1]
End point description: Percent reduction from baseline in serum TTR level at 6 months.	
End point type	Primary
End point timeframe: 6 months	

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: Limited collection of data due to the Sponsor's decision to terminate the study.

End point values	Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[2]			
Units: Percentage				

Notes:

[2] - Limited collection of data due to the Sponsor's decision to terminate the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred after the start of study drug administration on Day 0 (Baseline) up to 90 days post modified early termination visit (End of Study)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	Safety Population
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Reporting group description:

All patients who received at least 1 dose of study drug

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Investigations			
Blood immunoglobulin M increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercapnic coma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Dysphagia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
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	11 / 12 (91.67%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	6		
Injection site erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Injection site haematoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Generalised oedema			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Secretion discharge			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Anxiety subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Investigations			
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Prothrombin level decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood lactic acid increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood pyruvic acid increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood pressure abnormal subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Liver function test abnormal subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Injury, poisoning and procedural complications			
Thermal burn subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Tooth fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eschar subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Wound			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Cardiomyopathy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Speech disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aphasia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neuropathy peripheral			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Macrocytosis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Retinal vein occlusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Vomiting			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aerophagia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Dysuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Muscular weakness subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Arthralgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Back pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Joint stiffness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
Cystitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Oral herpes subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Bronchitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Metabolism and nutrition disorders			
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Hyperuricaemia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2016	The primary purpose for the protocol amendment is to allow for more intensive monitoring of liver function in response to adverse events (AEs) in ongoing and completed studies with revusiran in patients with transthyretin-mediated cardiac amyloidosis.
12 October 2016	The primary purpose of Protocol Amendment 3 is to provide guidance for follow-up of patients enrolled in the study following the Sponsor's decision to discontinue study drug dosing in all ongoing revusiran studies as previously communicated to the investigators, ethics committees, and health authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Safety and efficacy conclusions are limited due to Sponsor's decision to terminate the study.

Notes: