Clinical trial results:
A Phase 2, Open-label Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of ALN-TTRSC in Patients with Transthyretin (TTR) Cardiac Amyloidosis Who Have Previously Received ALN-TTRSC

Summary

EudraCT number	2014-001229-34
Trial protocol	GB
Global end of trial date	22 February 2017

Results information

Result version number	v1 (current)
This version publication date	09 March 2018
First version publication date	09 March 2018

Trial information

Trial identification

Sponsor protocol code	ALN-TTRSC-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02292186
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third St, 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	23 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2017
Global end of trial reached?	Yes
Global end of trial date	22 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of long-term dosing with ALN-TTRSC

Protection of trial subjects:

The safety assessments included the incidence and severity of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, thyroid function, coagulation and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, eye and physical examinations which were assessed and reviewed by the Medical Monitor throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 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: 9
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	25
EEA total number of subjects	9

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)	5
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 25 subjects who met entry criteria were enrolled.

Pre-assignment period milestones

Number of subjects started	25
Number of subjects completed	25

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:

All patients who received at least 1 dose of revusiran

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 of SC administered revusiran (on Day 0, 1, 2, 3, and 4) and a dose at Day 7. They were then to receive once weekly doses for the duration of the study, until termination of dosing.

Number of subjects in period 1	All Patients
Started	25
Completed	7
Not completed	18
Adverse event, serious fatal	6
Consent withdrawn by subject	2
Physician decision	1
Adverse event, non-fatal	4
Other	2
Progressive Disease	3

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	25	25	
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)	5	5	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	68.8		
standard deviation	± 6.47	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	22	22	
New York Heart Association Class Units: Subjects			
Class I	2	2	
Class II	17	17	
Class III	6	6	

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of revusiran

Reporting group values	Safety Analysis Set		
Number of subjects	25		
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)	5		
From 65-84 years	20		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	68.8		
standard deviation	± 6.47		
Gender categorical			
Units: Subjects			
Female	3		
Male	22		
New York Heart Association Class			
Units: Subjects			
Class I	2		
Class II	17		
Class III	6		

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description:	
All patients who received at least 1 dose of revusiran	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of revusiran	

Primary: Safety and tolerability of long-term dosing with ALN-TTRSC (revusiran) Transthyretin (TTR) Cardiac Amyloidosis patients

End point title	Safety and tolerability of long-term dosing with ALN-TTRSC (revusiran) Transthyretin (TTR) Cardiac Amyloidosis 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 90 days post modified early termination visit (end of study)	

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 number of patients completing the study make the data difficult to interpret.

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Number of Events				

Notes:

[2] - Limited number of patients completing the study make the data difficult to interpret.

Statistical analyses

No statistical analyses for this end point

Primary: Serum TTR levels

End point title	Serum TTR levels[3]
End point description:	

End point type	Primary
End point timeframe:	
Up to 90 days post modified early termination visit (end of study)	

Notes:

[3] - 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 number of patients completing the study make the data difficult to interpret.

End point values	All Patients			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: mg/L				
arithmetic mean (standard deviation)	()			

Notes:

[4] - Limited number of patients completing the study make the data difficult to interpret.

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

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 1 dose of revusiran in this study.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 25 (88.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Blood lactic acid increased			

subjects affected / exposed	3 / 25 (12.00%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QRS complex prolonged				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vasoplegia syndrome				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Congenital, familial and genetic disorders				
Cardiac failure acute				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac Failure				
subjects affected / exposed	6 / 25 (24.00%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				

subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiogenic shock				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Bradycardia				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Neuropathy peripheral				
subjects affected / exposed	7 / 25 (28.00%)			
occurrences causally related to treatment / all	5 / 8			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Constipation				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal ulcer				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Renal impairment				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Renal failure acute				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Obstructive uropathy				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure chronic				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Myopathy				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

Sepsis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 25 (4.00%)		
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	25 / 25 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		

Orthostatic hypotension subjects affected / exposed occurrences (all) Flushing subjects affected / exposed occurrences (all)	 4 / 25 (16.00%) 6 2 / 25 (8.00%) 8		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site pruritus subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Injection site swelling subjects affected / exposed occurrences (all) Injection site discolouration subjects affected / exposed occurrences (all) Injection site inflammation subjects affected / exposed occurrences (all) Injection site haematoma subjects affected / exposed occurrences (all)	 9 / 25 (36.00%) 13 8 / 25 (32.00%) 8 8 / 25 (32.00%) 41 6 / 25 (24.00%) 29 5 / 25 (20.00%) 14 4 / 25 (16.00%) 16 2 / 25 (8.00%) 2 2 / 25 (8.00%) 3 2 / 25 (8.00%) 3		
Reproductive system and breast disorders			

Erectile dysfunction subjects affected / exposed occurrences (all) Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rales subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	 12 / 25 (48.00%) 17 7 / 25 (28.00%) 10 5 / 25 (20.00%) 7 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 3 2 / 25 (8.00%) 2		
Investigations Weight decreased subjects affected / exposed occurrences (all)	 7 / 25 (28.00%) 9		

Blood lactic acid increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
International normalised ratio increased subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 8		
Liver function test abnormal subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4		
Vitamin A decreased subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Blood urea increased subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	10 / 25 (40.00%) 10		
Contusion subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4		
Excoriation subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Laceration subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Traumatic haematoma			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 25 (28.00%)		
occurrences (all)	7		
Cardiac failure			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Pericardial effusion			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 25 (40.00%)		
occurrences (all)	14		
Neuropathy peripheral			
subjects affected / exposed	9 / 25 (36.00%)		
occurrences (all)	12		
Headache			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 25 (36.00%)		
occurrences (all)	10		
Diarrhoea			

subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6		
Nausea subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5		
Abdominal distension subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3		
Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Vomiting subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 4		
Increased tendency to bruise subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Pruritus subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Decubitus ulcer subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Renal and urinary disorders			
Renal failure acute subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 5		
Urinary retention subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Musculoskeletal and connective tissue disorders			

Muscle spasms			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Joint swelling			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Carpal tunnel syndrome			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Intervertebral disc degeneration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 25 (28.00%)		
occurrences (all)	8		
Lower respiratory tract infection			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	5		
Pneumonia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Tooth infection			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Onychomycosis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Fluid overload			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gout			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2014	Updated the exclusion criteria
23 October 2014	The primary purpose of the amendment is to allow for patient/caregiver administration of the study drug at home between clinic visits without the need for administration by a home healthcare provider.
25 March 2016	The primary purpose for the protocol amendment is to extend the duration of the study from 2 years to 4 years to provide long-term evaluation of revusiran. Additionally, in response to adverse events (AEs) observed in ongoing and completed studies with revusiran in patients with transthyretin-mediated cardiac amyloidosis, more intensive monitoring of liver function is incorporated into the protocol.
12 October 2016	Provided guidance to the Investigator for follow-up of patients enrolled in the study following the Sponsor’s decision to discontinue study drug dosing in all ongoing revusiran studies

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 data are difficult to interpret due to the limited numbers of patients completing the study.

Notes: