Clinical trial results:
A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN TTRSC in Patients With Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC)

Summary

EudraCT number	2014-003835-20
Trial protocol	GB SE DE ES BE IT
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	12 April 2018
First version publication date	12 April 2018

Trial information

Trial identification

Sponsor protocol code	ALN-TTRSC-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02319005
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. , 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	12 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of ALN-TTRSC (revusiran) in patients with familial amyloidotic cardiomyopathy (FAC), hereafter referred to as hereditary transthyretin (TTR)-mediated cardiac amyloidosis (hATTR cardiac amyloidosis).

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) was implemented for the study and operated under a prespecified charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 December 2014
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	Spain: 3
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	United States: 136
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	206
EEA total number of subjects	65

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)	66
From 65 to 84 years	139
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 206 patients with hATTR cardiac amyloidosis were enrolled and randomized in the study.

Pre-assignment period milestones

Number of subjects started	206
Number of subjects completed	206

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Revusiran

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 500 mg revusiran or placebo daily for 5 days during the first week, a single dose on Day 7, and then once weekly for up to 18 months.

Arm title	Placebo

Arm description:

All patients who received at least 1 dose of placebo.

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received placebo daily for 5 days during the first week, a single dose on Day 7, and then once weekly for up to 18 months.

Number of subjects in period 1	Revusiran	Placebo
Started	140	66
Completed	92	51
Not completed	48	15
Adverse event, serious fatal	20	7
Consent withdrawn by subject	9	7
Physician decision	2	-
Adverse event, non-fatal	9	-
Other	5	1
Due to Study Termination	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Revusiran
Reporting group description:	
All patients who received at least 1 dose of revusiran	
Reporting group title	Placebo
Reporting group description:	
All patients who received at least 1 dose of placebo.	

Reporting group values	Revusiran	Placebo	Total
Number of subjects	140	66	206
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	25	66
From 65-84 years	98	41	139
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	68.6	66.2	
standard deviation	± 9.28	± 9.54	-
Gender categorical Units: Subjects			
Female	35	13	48
Male	105	53	158
New York Heart Association Class Units: Subjects			
Class I	13	4	17
Class II	83	42	125
Class III	44	20	64

Subject analysis sets	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients that were treated and received at least 1 dose of the study drug.	

Reporting group values	Safety		
Number of subjects	206		
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)	66		
From 65-84 years	139		
85 years and over	1		
Age continuous Units: years			
arithmetic mean	67.8		
standard deviation	± 9.40		
Gender categorical Units: Subjects			
Female	48		
Male	158		
New York Heart Association Class Units: Subjects			
Class I	17		
Class II	125		
Class III	64		

End points

End points reporting groups

Reporting group title	Revusiran
Reporting group description:	
All patients who received at least 1 dose of revusiran	
Reporting group title	Placebo
Reporting group description:	
All patients who received at least 1 dose of placebo.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients that were treated and received at least 1 dose of the study drug.	

Primary: 6-Minute Walk Test

End point title	6-Minute Walk Test[1]
End point description:	
The difference between the revusiran and placebo group in change from baseline to 18 months in the total distance walked in 6 minutes	
End point type	Primary
End point timeframe:	
From baseline to 18 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: meter				
arithmetic mean (standard error)	()			

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

Primary: Serum TTR Reduction

End point title	Serum TTR Reduction[3]
End point description:	
The difference between revusiran (ALN-TTRSC) and placebo group in the percent reduction in serum TTR levels over 18 months	
End point type	Primary
End point timeframe:	
From baseline to 18 months	

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 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[4]			
Units: meter				
arithmetic mean (standard error)	()			

Notes:

[4] - 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Revusiran

Reporting group description:

All patients who received at least 1 dose of revusiran

Reporting group title	Placebo

Reporting group description:

All patients who received at least 1 dose of placebo.

Serious adverse events	Revusiran	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 140 (59.29%)	34 / 66 (51.52%)	
number of deaths (all causes)	23	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder cancer			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to biliary tract			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 140 (2.14%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			

subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lipoma excision			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 140 (0.71%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Asthenia			
subjects affected / exposed	1 / 140 (0.71%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 140 (0.71%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug administration error			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	25 / 140 (17.86%)	9 / 66 (13.64%)	
occurrences causally related to treatment / all	2 / 35	0 / 13	
deaths causally related to treatment / all	2 / 5	0 / 0	
Cardiac failure acute			
subjects affected / exposed	15 / 140 (10.71%)	9 / 66 (13.64%)	
occurrences causally related to treatment / all	1 / 20	0 / 12	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	9 / 140 (6.43%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	4 / 12	0 / 6	
deaths causally related to treatment / all	1 / 4	0 / 2	
Atrial fibrillation			
subjects affected / exposed	7 / 140 (5.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 140 (1.43%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	4 / 140 (2.86%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac arrest			
subjects affected / exposed	3 / 140 (2.14%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 140 (0.71%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	1 / 140 (0.71%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			

subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	7 / 140 (5.00%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 140 (2.86%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 140 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen disorder			

subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	3 / 140 (2.14%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 140 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 140 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal amyloidosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumobilia			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	5 / 140 (3.57%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	3 / 140 (2.14%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 140 (0.71%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Chronic			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			

subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 140 (2.14%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective tenosynovitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 140 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 140 (2.14%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			

subjects affected / exposed	4 / 140 (2.86%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 140 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	2 / 140 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 140 (0.71%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	2 / 140 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 140 (0.71%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Revusiran	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 140 (95.71%)	61 / 66 (92.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 140 (7.86%)	4 / 66 (6.06%)	
occurrences (all)	15	4	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	23 / 140 (16.43%)	4 / 66 (6.06%)	
occurrences (all)	101	13	
Injection site erythema			
subjects affected / exposed	16 / 140 (11.43%)	0 / 66 (0.00%)	
occurrences (all)	64	0	
Fatigue			
subjects affected / exposed	14 / 140 (10.00%)	8 / 66 (12.12%)	
occurrences (all)	16	32	
Oedema peripheral			
subjects affected / exposed	25 / 140 (17.86%)	12 / 66 (18.18%)	
occurrences (all)	30	16	
Asthenia			
subjects affected / exposed	15 / 140 (10.71%)	2 / 66 (3.03%)	
occurrences (all)	18	2	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	25 / 140 (17.86%)	10 / 66 (15.15%)	
occurrences (all)	29	14	
Dyspnoea			
subjects affected / exposed	16 / 140 (11.43%)	9 / 66 (13.64%)	
occurrences (all)	22	9	
Productive cough			
subjects affected / exposed	9 / 140 (6.43%)	1 / 66 (1.52%)	
occurrences (all)	9	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 140 (5.71%)	2 / 66 (3.03%)	
occurrences (all)	8	2	
Investigations			
Weight decreased			
subjects affected / exposed	12 / 140 (8.57%)	4 / 66 (6.06%)	
occurrences (all)	14	5	
Blood lactic acid increased			
subjects affected / exposed	15 / 140 (10.71%)	3 / 66 (4.55%)	
occurrences (all)	16	3	
Blood bilirubin increased			
subjects affected / exposed	10 / 140 (7.14%)	4 / 66 (6.06%)	
occurrences (all)	11	4	
Liver function test abnormal			
subjects affected / exposed	12 / 140 (8.57%)	1 / 66 (1.52%)	
occurrences (all)	12	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 140 (7.14%)	5 / 66 (7.58%)	
occurrences (all)	16	9	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	10 / 140 (7.14%)	3 / 66 (4.55%)	
occurrences (all)	14	3	
Atrial fibrillation			

subjects affected / exposed	16 / 140 (11.43%)	2 / 66 (3.03%)	
occurrences (all)	20	3	
Cardiac failure congestive			
subjects affected / exposed	4 / 140 (2.86%)	6 / 66 (9.09%)	
occurrences (all)	4	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 140 (12.86%)	13 / 66 (19.70%)	
occurrences (all)	19	15	
Neuropathy peripheral			
subjects affected / exposed	20 / 140 (14.29%)	6 / 66 (9.09%)	
occurrences (all)	21	6	
Hypoaesthesia			
subjects affected / exposed	12 / 140 (8.57%)	4 / 66 (6.06%)	
occurrences (all)	21	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	20 / 140 (14.29%)	11 / 66 (16.67%)	
occurrences (all)	23	13	
Nausea			
subjects affected / exposed	20 / 140 (14.29%)	5 / 66 (7.58%)	
occurrences (all)	28	7	
Vomiting			
subjects affected / exposed	9 / 140 (6.43%)	5 / 66 (7.58%)	
occurrences (all)	18	7	
Abdominal pain			
subjects affected / exposed	7 / 140 (5.00%)	3 / 66 (4.55%)	
occurrences (all)	10	5	
Diarrhoea			
subjects affected / exposed	9 / 140 (6.43%)	5 / 66 (7.58%)	
occurrences (all)	9	5	
Abdominal pain upper			
subjects affected / exposed	9 / 140 (6.43%)	1 / 66 (1.52%)	
occurrences (all)	9	1	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	9 / 140 (6.43%)	2 / 66 (3.03%)	
occurrences (all)	9	2	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	9 / 140 (6.43%)	1 / 66 (1.52%)	
occurrences (all)	9	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	14 / 140 (10.00%)	8 / 66 (12.12%)	
occurrences (all)	19	9	
Arthralgia			
subjects affected / exposed	9 / 140 (6.43%)	6 / 66 (9.09%)	
occurrences (all)	10	8	
Muscle spasms			
subjects affected / exposed	9 / 140 (6.43%)	2 / 66 (3.03%)	
occurrences (all)	11	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 140 (7.86%)	5 / 66 (7.58%)	
occurrences (all)	11	5	
Bronchitis			
subjects affected / exposed	10 / 140 (7.14%)	3 / 66 (4.55%)	
occurrences (all)	11	3	
Sinusitis			
subjects affected / exposed	7 / 140 (5.00%)	3 / 66 (4.55%)	
occurrences (all)	8	4	
Upper respiratory tract infection			
subjects affected / exposed	8 / 140 (5.71%)	4 / 66 (6.06%)	
occurrences (all)	8	4	
Urinary tract infection			
subjects affected / exposed	8 / 140 (5.71%)	2 / 66 (3.03%)	
occurrences (all)	8	4	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	6 / 140 (4.29%)	8 / 66 (12.12%)	
occurrences (all)	10	12	
Decreased appetite			
subjects affected / exposed	13 / 140 (9.29%)	6 / 66 (9.09%)	
occurrences (all)	16	6	
Gout			
subjects affected / exposed	3 / 140 (2.14%)	7 / 66 (10.61%)	
occurrences (all)	4	16	
Fluid overload			
subjects affected / exposed	6 / 140 (4.29%)	4 / 66 (6.06%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	The primary purpose for the protocol amendment is to update eligibility criteria related to confirmation of amyloid tissue deposition and liver function. These changes do not alter the originally intended patient population. Additionally, in response to adverse events (AEs) observed during the study, more intensive monitoring of liver function is incorporated into the protocol. A dose reduction allowance for significant injection site reactions (ISRs) and liver function test (LFT) abnormalities is also included.
11 October 2016	Provided 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

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.

Study drug was discontinued early due to an imbalance in mortality observed between patients treated with revusiran and placebo. Given the limited exposure to study drug, clinical efficacy conclusions cannot be drawn.

Notes: