



## Clinical trial results:

### An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant

#### Summary

EudraCT number	2018-003519-24
Trial protocol	GB FR PT DE ES IT
Global end of trial date	20 October 2020

#### Results information

Result version number	v1 (current)
This version publication date	05 November 2021
First version publication date	05 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	ALN-TTR02-008
-----------------------	---------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03862807
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	675 West Kendall Street, Cambridge, United States, 02142
Public contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc, +1 18772569526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc, +1 8772569526, 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	20 October 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 October 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of patisiran in subjects with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) with disease progression after liver transplant.

Protection of trial subjects:

A safety review committee was not utilized for this study; however, a transplant hepatologist was available for consultation on an as needed basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2019
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	Portugal: 3
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	23
EEA total number of subjects	22

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	17
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) with disease progression post-orthotopic liver transplant were enrolled at nine sites in France, Germany, Italy, Portugal, Spain, Sweden and the United Kingdom.

### Pre-assignment

Screening details:

Subjects were screened to ensure that they met all the inclusion criteria and none of the exclusion criteria. Subjects demographic data and medical history/disease history were obtained. Medical history captured transplant history and evidence of disease progression.

### Pre-assignment period milestones

Number of subjects started	24 <sup>[1]</sup>
Number of subjects completed	23

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Receive Treatment: 1
----------------------------	------------------------------

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject stopped study participation after enrollment but prior to the first dose of patisiran due to failure to meet one of the eligibility criteria.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Patisiran
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Patisiran
Investigational medicinal product code	
Other name	ONPATTRO, ALN-TTR02
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received patisiran 0.3 milligrams/kilogram (mg/kg) via intravenous (IV) infusion once every 3 weeks (q3w) for 12 months. Dosing was based on actual body weight. For subjects weighing 100 kg or more, patisiran was administered at a total dose of 30 mg IV q3w.

<b>Number of subjects in period 1</b>	Patisiran
Started	23
Completed Treatment	22 <sup>[2]</sup>
Completed	23

---

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One subject discontinued treatment with patisiran but continued to undergo study assessments and completed the study.

## Baseline characteristics

### Reporting groups

Reporting group title	Patisiran
-----------------------	-----------

Reporting group description: -

Reporting group values	Patisiran	Total	
Number of subjects	23	23	
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	6	6	
Age continuous			
Units: years			
arithmetic mean	58.1		
standard deviation	± 9.9	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	13	13	
Race			
Units: Subjects			
White	22	22	
Asian	1	1	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	23	23	
TTR			
Units: mg/L			
median	192.140		
full range (min-max)	123.74 to 315.12	-	

## End points

### End points reporting groups

Reporting group title	Patisiran
Reporting group description: -	

### Primary: Average of Month 6 and Month 12 Percentage Reduction From Baseline in Serum Transthyretin (TTR)

End point title	Average of Month 6 and Month 12 Percentage Reduction From Baseline in Serum Transthyretin (TTR) <sup>[1]</sup>
-----------------	--

End point description:

Serum TTR was assessed using enzyme linked immunosorbent assay (ELISA).

Analysis population was subjects from the Safety Analysis Set, all subjects who received any amount of patisiran, with post-baseline TTR assessments collected within 24 days (inclusive) after receiving a complete dose of patisiran.

End point type	Primary
----------------	---------

End point timeframe:

Baseline, Months 6 and 12

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: The reported data in the endpoint is the statistical analysis data.

End point values	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: TTR percent reduction from baseline				
median (confidence interval 95%)	91.0 (86.1 to 92.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Neuropathy Impairment Score (NIS) at Month 12

End point title	Change From Baseline in the Neuropathy Impairment Score (NIS) at Month 12
-----------------	---

End point description:

The NIS is a composite neurologic impairment score that assesses motor weakness (NIS-W), sensation (NIS-S) and reflexes (NIS-R) by physical exam. The minimum and maximum values are 0 and 244, respectively. A higher score indicates a worse outcome.

Analysis population was subjects from the Per Protocol (PP) Analysis Set, all subjects in the Safety Analysis Set who missed  $\leq 2$  doses of patisiran due to the COVID-19 pandemic during the study, with NIS data available at Month 12.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 12

<b>End point values</b>	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: score on a scale				
arithmetic mean (standard error)	-3.7 ( $\pm$ 2.7)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Score at Month 12

End point title	Change From Baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) Score at Month 12
-----------------	--

End point description:

The Norfolk QoL-DN questionnaire is a standardized 35-item patient-reported outcomes measure that is sensitive to the different features of diabetic neuropathy - small fiber, large fiber, and autonomic nerve function. The minimum and maximum values are -4 and 136, respectively. A higher score indicates a worse outcome.

Analysis population is the PP Analysis Set: All subjects in the Safety Analysis Set who missed  $\leq 2$  doses of patisiran due to the COVID-19 pandemic during the study.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 12

<b>End point values</b>	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: score on a scale				
arithmetic mean (standard error)	-6.5 ( $\pm$ 4.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Rasch-Built Overall Disability Scale (R-ODS) at Month 12

End point title	Change From Baseline in the Rasch-Built Overall Disability Scale (R-ODS) at Month 12
-----------------	--



End point description:

The R-ODS is comprised of a 24-item linearly weighted scale that specifically captures activity and social participation limitations. The minimum and maximum values are 0 and 48, respectively. A higher score indicates a better outcome.

Analysis population was the PP Analysis Set: All subjects in the Safety Analysis Set who missed  $\leq 2$  doses of patisiran due to the COVID-19 pandemic during the study.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 12

End point values	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: score on a scale				
arithmetic mean (standard error)	-0.1 ( $\pm$ 1.1)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Composite Autonomic Symptom Score (COMPASS-31) at Month 12

End point title	Change From Baseline in the Composite Autonomic Symptom Score (COMPASS-31) at Month 12
-----------------	--

End point description:

The COMPASS-31 questionnaire is a measure of autonomic neuropathy symptoms. The questions evaluate 6 autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor). The minimum and maximum values are 0 and 100, respectively. A higher score indicates a worse outcome.

Analysis population was PP) Analysis Set, all subjects in the Safety Analysis Set who missed  $\leq 2$  doses of patisiran due to the COVID-19 pandemic during the study, with COMPASS-31 data available at Month 12.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 12

End point values	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: score on a scale				
least squares mean (standard error)	-5.0 ( $\pm$ 2.6)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Modified Body Mass Index (mBMI) at Month 12

End point title	Change From Baseline in the Modified Body Mass Index (mBMI) at Month 12
-----------------	---

End point description:

Nutritional status of subjects was evaluated using the mBMI, calculated as BMI (kg/m<sup>2</sup>) multiplied by albumin (g/L). An increase from baseline in mBMI suggests improvement, and a decrease from baseline suggests worsening.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, Month 12

End point values	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: kg/m <sup>2</sup> x albumin g/L				
arithmetic mean (standard error)	4.4 (± 21.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events
-----------------	--

End point description:

An AE is any untoward medical occurrence in a subject or clinical investigational patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Analysis population was the Safety Analysis Set: All subjects who received any amount of patisiran.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to end of study at Month 13

End point values	Patisiran			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of subjects				
number (not applicable)	100			

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at Month 13.

Adverse event reporting additional description:

Safety Analysis Set: All participants who received any amount of patisiran.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.0
--------------------	------

### Reporting groups

Reporting group title	Patisiran
-----------------------	-----------

Reporting group description:

Subjects received patisiran 0.3 milligrams/kilogram (mg/kg) via intravenous (IV) infusion once every 3 weeks (q3w) for 12 months. Dosing was based on actual body weight. For subjects weighing 100 kg or more, patisiran was administered at a total dose of 30 mg IV q3w.

Serious adverse events	Patisiran		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Syncope			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 23 (4.35%)		
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 %

<b>Non-serious adverse events</b>	Patisiran		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Skin laceration			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Vascular disorders			
Poor venous access			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Oedema peripheral			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 23 (21.74%)</p> <p>10</p> <p>3 / 23 (13.04%)</p> <p>3</p>		
<p>Ear and labyrinth disorders</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 23 (8.70%)</p> <p>2</p>		
<p>Immune system disorders</p> <p>Infusion related reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 23 (26.09%)</p> <p>65</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bile acid malabsorption</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 23 (8.70%)</p> <p>2</p> <p>2 / 23 (8.70%)</p> <p>2</p> <p>8 / 23 (34.78%)</p> <p>14</p>		
<p>Renal and urinary disorders</p> <p>Oliguria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 23 (8.70%)</p> <p>2</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 23 (21.74%)</p> <p>5</p>		
<p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cystitis</p>	<p>2 / 23 (8.70%)</p> <p>2</p>		

subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported