



Clinical trial results:

A Phase 1/2, Single-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose Safety, Tolerability, Pharmacokinetic and Pharmacodynamics Study of Subcutaneously Administered ALN-GO1 in Healthy Adult Subjects, and Patients with Primary Hyperoxaluria Type 1 Summary

EudraCT number	2015-004407-23
Trial protocol	GB DE NL
Global end of trial date	23 January 2019

Results information

Result version number	v2 (current)
This version publication date	07 February 2020
First version publication date	21 August 2019
Version creation reason	• Correction of full data set - Inclusion of data for a secondary outcome measure.

Trial information

Trial identification

Sponsor protocol code	ALN-GO1-001
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02706886
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, +1 866330 0326, Investors@alnylam.com
Scientific contact	Chief Medical Officer, Alnylam Pharmaceuticals Inc, +1 866330 0326, medinfo@alnylam.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002079-PIP01-16
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 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of single and multiple ascending doses of lumasiran (ALN-GO1), respectively, in healthy adult subjects and in patients with primary hyperoxaluria type 1 (PH1).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy:

Subjects with PH1 were required to continue their individual standard of care regimen.

Evidence for comparator: -

Actual start date of recruitment	08 March 2016
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	Israel: 7
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	52
EEA total number of subjects	45

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)	10

Adolescents (12-17 years)	6
Adults (18-64 years)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at nine sites in Germany, France, the United Kingdom, Israel, and the Netherlands.

Pre-assignment

Screening details:

Fifty-two subjects were enrolled in this study. In Part A, single ascending dose (SAD), 32 healthy adults were dosed and in Part B, multiple ascending doses (MAD), 20 adult and paediatric subjects with PH1 were dosed.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A: SAD: Placebo

Arm description:

A single dose of matching placebo was administered.

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

Dosage and administration details:

Matching placebo (Sterile saline: 0.9% sodium chloride [NaCl]) was administered subcutaneously (SC) on Day 1.

Arm title	Part A: SAD: Lumasiran 0.3 mg/kg
------------------	----------------------------------

Arm description:

A single dose of 0.3 mg/kg lumasiran was administered.

Arm type	Experimental
Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lumasiran was administered SC on Day 1.

Arm title	Part A: SAD: Lumasiran 1.0 mg/kg
------------------	----------------------------------

Arm description:

A single dose of 1.0 mg/kg lumasiran was administered.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Lumasiran was administered SC on Day 1.	
Arm title	Part A: SAD: Lumasiran 3.0 mg/kg
Arm description: A single dose of 3.0 mg/kg lumasiran was administered.	
Arm type	Experimental
Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Lumasiran was administered SC on Day 1.	
Arm title	Part A: SAD: Lumasiran 6.0 mg/kg
Arm description: A single dose of 6.0 mg/kg lumasiran was administered.	
Arm type	Experimental
Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Lumasiran was administered SC on Day 1.	
Arm title	Part B: MAD: Placebo
Arm description: Subjects with PH1 were treated with placebo matching one of the lumasiran dosages (one placebo subject for each lumasiran arm) in Part B. At Day 85 these placebo-treated subjects crossed over to their respective Part B lumasiran arms.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Matching placebo (sterile saline: 0.9% sodium chloride [NaCl]) was administered subcutaneously (SC) on Days 1, 29 and 57 for qM and Day 1 for q3M.	
Arm title	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)
Arm description: Subjects with PH1 were treated with 1.0 mg/kg lumasiran qM.	
Arm type	Experimental

Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lumasiran was administered SC on Days 1, 29 and 57.

Arm title	Part B: MAD: Lumasiran 3.0 mg/kg qM
------------------	-------------------------------------

Arm description:

Subjects with PH1 were treated with 3.0 mg/kg lumasiran qM.

Arm type	Experimental
Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lumasiran was administered SC on Days 1, 29 and 57.

Arm title	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
------------------	--

Arm description:

Subjects with PH1 were treated with 3.0 mg/kg lumasiran q3M.

Arm type	Experimental
Investigational medicinal product name	Lumasiran
Investigational medicinal product code	
Other name	ALN-GO1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lumasiran was administered SC on Days 1 and 85.

Number of subjects in period 1	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg
Started	8	6	6
Completed	8	6	6
Not completed	0	0	0
Withdrawal by subject	-	-	-

Number of subjects in period 1	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Placebo
Started	6	6	3
Completed	4	6	3
Not completed	2	0	0
Withdrawal by subject	2	-	-

Number of subjects in period 1	Part B: MAD: Lumasiran 1.0 mg/kg once monthly	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3

	(qM)		months (q3M)
Started	8	8	4
Completed	8	8	4
Not completed	0	0	0
Withdrawal by subject	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: SAD: Placebo
Reporting group description: A single dose of matching placebo was administered.	
Reporting group title	Part A: SAD: Lumasiran 0.3 mg/kg
Reporting group description: A single dose of 0.3 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 1.0 mg/kg
Reporting group description: A single dose of 1.0 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 3.0 mg/kg
Reporting group description: A single dose of 3.0 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 6.0 mg/kg
Reporting group description: A single dose of 6.0 mg/kg lumasiran was administered.	
Reporting group title	Part B: MAD: Placebo
Reporting group description: Subjects with PH1 were treated with placebo matching one of the lumasiran dosages (one placebo subject for each lumasiran arm) in Part B. At Day 85 these placebo-treated subjects crossed over to their respective Part B lumasiran arms.	
Reporting group title	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)
Reporting group description: Subjects with PH1 were treated with 1.0 mg/kg lumasiran qM.	
Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg qM
Reporting group description: Subjects with PH1 were treated with 3.0 mg/kg lumasiran qM.	
Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Reporting group description: Subjects with PH1 were treated with 3.0 mg/kg lumasiran q3M.	

Reporting group values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg
Number of subjects	8	6	6
Age categorical			
Units: Subjects			

Age continuous			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: years			
arithmetic mean	29.8	28.8	30.2
standard deviation	± 6.25	± 7.36	± 7.81
Gender categorical			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: Subjects			
Female	5	0	3

Male	3	6	3
------	---	---	---

Reporting group values	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Placebo
Number of subjects	6	6	3
Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: years			
arithmetic mean	27.3	28.8	20.7
standard deviation	± 3.44	± 5.46	± 19.40
Gender categorical			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: Subjects			
Female	3	5	1
Male	3	1	2

Reporting group values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Number of subjects	8	8	4
Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: years			
arithmetic mean	13.3	14.9	18.0
standard deviation	± 9.44	± 7.47	± 17.26
Gender categorical			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: Subjects			
Female	7	4	2
Male	1	4	2

Reporting group values	Total		
Number of subjects	52		
Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: years			

arithmetic mean			
standard deviation	-		

Gender categorical			
Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.			
Units: Subjects			
Female	29		
Male	23		

End points

End points reporting groups

Reporting group title	Part A: SAD: Placebo
Reporting group description: A single dose of matching placebo was administered.	
Reporting group title	Part A: SAD: Lumasiran 0.3 mg/kg
Reporting group description: A single dose of 0.3 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 1.0 mg/kg
Reporting group description: A single dose of 1.0 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 3.0 mg/kg
Reporting group description: A single dose of 3.0 mg/kg lumasiran was administered.	
Reporting group title	Part A: SAD: Lumasiran 6.0 mg/kg
Reporting group description: A single dose of 6.0 mg/kg lumasiran was administered.	
Reporting group title	Part B: MAD: Placebo
Reporting group description: Subjects with PH1 were treated with placebo matching one of the lumasiran dosages (one placebo subject for each lumasiran arm) in Part B. At Day 85 these placebo-treated subjects crossed over to their respective Part B lumasiran arms.	
Reporting group title	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)
Reporting group description: Subjects with PH1 were treated with 1.0 mg/kg lumasiran qM.	
Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg qM
Reporting group description: Subjects with PH1 were treated with 3.0 mg/kg lumasiran qM.	
Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Reporting group description: Subjects with PH1 were treated with 3.0 mg/kg lumasiran q3M.	

Primary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs) ^[1]
End point description: An AE is any untoward medical occurrence in a clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.	
End point type	Primary
End point timeframe: Part A (SAD phase): Up to 405 days; Part B (MAD phase): Up to 546 days	
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: Only descriptive data were planned to be reported for this safety endpoint.	

End point values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	6
Units: subjects	5	6	2	6

End point values	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	8	8
Units: subjects	6	2	8	7

End point values	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Lumasiran in Plasma

End point title	Maximum Concentration (Cmax) of Lumasiran in Plasma ^[2]
-----------------	--

End point description:

Pharmacokinetic (PK) Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups.

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

End point timeframe:

Part A (SAD phase): Day 1: predose, 30 minutes (min), 1 hour (h), 2 h, 4 h, 6 h, 8 h and 24 h; Part B (MAD phase): Days 1 and 57 for qM dosing and Days 1 and 85 for q3M dosing: predose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 h

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacokinetic (PK) endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,6,8,8,4)	39.7940 (± 8.58882)	204.3748 (± 111.68091)	533.4527 (± 160.11060)	1176.1302 (± 199.89797)
Day 57 (n=0,0,0,0,8,8,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

End point values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	4	
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,6,8,8,4)	324.1386 (± 489.71104)	582.4515 (± 266.90105)	432.2798 (± 245.02660)	
Day 57 (n=0,0,0,0,8,8,0)	147.6780 (± 67.97968)	701.1708 (± 511.63001)	9999 (± 9999)	
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	411.5613 (± 174.92146)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (tmax) of Lumasiran in Plasma

End point title	Time to Cmax (tmax) of Lumasiran in Plasma ^[3]
-----------------	---

End point description:

PK Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups.

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

End point timeframe:

Part A (SAD phase): Day 1: predose, 30 minutes (min), 1 hour (h), 2 h, 4 h, 6 h, 8 h and 24 h; Part B (MAD phase): Days 1 and 57 for qM dosing and Days 1 and 85 for q3M dosing: predose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 h

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hours				
median (full range (min-max))				
Day 1 (n=6,6,6,6,8,8,4)	5.0167 (4.000 to 8.017)	1.5000 (0.517 to 8.000)	3.0000 (0.500 to 8.000)	7.0000 (0.500 to 8.067)
Day 57 (n=0,0,0,0,8,8,0)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)
Day 85 (n=0,0,0,0,0,0,3)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)

End point values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	4	
Units: hours				
median (full range (min-max))				
Day 1 (n=6,6,6,6,8,8,4)	3.9917 (0.567 to 5.967)	4.9917 (0.533 to 12.000)	9.0000 (5.783 to 12.017)	
Day 57 (n=0,0,0,0,8,8,0)	3.0417 (0.500 to 6.000)	2.9833 (0.500 to 8.000)	9999 (9999 to 9999)	
Day 85 (n=0,0,0,0,0,0,3)	9999 (9999 to 9999)	9999 (9999 to 9999)	5.9833 (4.050 to 7.950)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-last) of Lumasiran in Plasma

End point title	Area Under the Concentration-Time Curve from Time 0 to Time of Last Measurable Concentration (AUC0-last) of Lumasiran in Plasma ^[4]
-----------------	--

End point description:

PK Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups.

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

End point timeframe:

Part A (SAD phase): predose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 24 h; Part B (MAD phase): Starting on Days 1, 57, 85, and 141 (q3M only Days 1 and 85): predose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 h

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,6,8,8,4)	293.5232 (± 96.86989)	1899.8119 (± 558.25326)	7211.5890 (± 1125.64173)	16778.0579 (± 4380.15325)
Day 57 (n=0,0,0,0,8,8,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

End point values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	4	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,6,8,8,4)	1428.0412 (± 697.85233)	7400.2181 (± 2331.89843)	6337.9082 (± 3840.03340)	
Day 57 (n=0,0,0,0,8,8,0)	1608.1457 (± 708.95156)	7959.7873 (± 1726.57675)	9999 (± 9999)	
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	5136.3462 (± 2757.90139)	

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t_{1/2}) of Lumasiran in Plasma

End point title	Terminal Half-life (t _{1/2}) of Lumasiran in Plasma ^[5]
-----------------	--

End point description:

PK Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups. 99999 = SD was not calculated for arms with data for 1 subject.

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

End point timeframe:

Part A (SAD phase): Day 1: predose, 30 minutes (min), 1 hour (h), 2 h, 4 h, 6 h, 8 h and 24 h; Part B (MAD phase): Days 1 and 57 for qM dosing and Days 1 and 85 for q3M dosing: predose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 48 h

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	8
Units: hours				
arithmetic mean (standard deviation)				
Day 1 (n=2,2,1,4,5,1)	7.0655 (± 0.37379)	5.9798 (± 1.52471)	3.4683 (± 99999)	3.2670 (± 1.52759)
Day 57 (n=0,0,0,0,4,4,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	7.8090 (± 4.52009)
Day 85 (n=0,0,0,0,0,0,1)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

End point values	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: hours				
arithmetic mean (standard deviation)				
Day 1 (n=2,2,1,4,5,1)	5.4574 (± 3.49432)	7.8028 (± 99999)		
Day 57 (n=0,0,0,0,4,4,0)	5.8356 (± 3.12156)	9999 (± 9999)		
Day 85 (n=0,0,0,0,0,0,1)	9999 (± 9999)	4.6694 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fraction Excreted in Urine in 24 Hours (Fe0-24) of Lumasiran

End point title	Fraction Excreted in Urine in 24 Hours (Fe0-24) of Lumasiran ^[6]
-----------------	---

End point description:

PK Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups.

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

End point timeframe:

Part A (SAD): Day 1: pooled urine 0-4 h, 4-8 h and 8-24 h; Part B (MAD): Part B (MAD phase): Days 1 and 57 for qM dosing and Days 1 and 85 for q3M dosing: pooled urine 0-4 h, 4-8 h, 8-12 h and 12-24 h

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: percentage of fractional excretion				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,5,7,7,4)	17.4219 ($\pm$ 2.44129)	19.0713 ($\pm$ 3.88914)	21.0472 ($\pm$ 5.36667)	25.7931 ($\pm$ 3.25937)
Day 57 (n=0,0,0,0,8,6,0)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)
Day 85 (n=0,0,0,0,0,0,3)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)

End point values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	4	
Units: percentage of fractional excretion				
arithmetic mean (standard deviation)				
Day 1 (n=6,6,6,5,7,7,4)	11.0895 ($\pm$ 3.74207)	11.1877 ($\pm$ 6.07719)	7.1691 ($\pm$ 2.37465)	
Day 57 (n=0,0,0,0,8,6,0)	9.4698 ($\pm$ 4.21949)	12.4604 ($\pm$ 4.02897)	9999 ($\pm$ 9999)	
Day 85 (n=0,0,0,0,0,0,3)	9999 ($\pm$ 9999)	9999 ($\pm$ 9999)	13.6938 ($\pm$ 3.60004)	

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Clearance (CLR) of Lumasiran

End point title	Renal Clearance (CLR) of Lumasiran ^[7]
-----------------	---

End point description:

PK Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of lumasiran and had at least 1 postdose sample for PK parameters and who had evaluable PK data. In each row header within the table n indicates the number of subjects analysed for the specific time point. Here, 9999 = Not Applicable: Data for Part A were collected only on Day 1; Part B on Days 1 and 57 for qM and on Days 1 and 85 for q3M arm groups. 99999 = SD was not calculated for arms with data for 1 subject.

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

End point timeframe:

Part A (SAD): Day 1: pooled urine 0-4 h, 4-8 h and 8-24 h; Part B (MAD): Part B (MAD phase): Days 1 and 57 for qM dosing and Days 1 and 85 for q3M dosing: pooled urine 0-4 h, 4-8 h, 8-12 h and 12-24 h

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK endpoints were only determined in subjects treated with lumasiran.

End point values	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Liter/hour (L/h)				
arithmetic mean (standard deviation)				
Day 1 (n=1,5,6,5,6,6,4)	8.7817 (± 99999)	5.4906 (± 2.07402)	5.8211 (± 1.31377)	6.3417 (± 1.15497)
Day 57 (n=0,0,0,0,7,6,0)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

End point values	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	4	
Units: Liter/hour (L/h)				
arithmetic mean (standard deviation)				
Day 1 (n=1,5,6,5,6,6,4)	2.2612 (± 1.17616)	2.3818 (± 1.13067)	2.0564 (± 1.20600)	
Day 57 (n=0,0,0,0,7,6,0)	1.9610 (± 1.11228)	2.5150 (± 0.80386)	9999 (± 9999)	
Day 85 (n=0,0,0,0,0,0,3)	9999 (± 9999)	9999 (± 9999)	3.3663 (± 1.18371)	

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Plasma Glycolate Concentration

End point title	Baseline Plasma Glycolate Concentration ^[8]
End point description:	
Pharmacodynamic (PD) Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. Due to a quality issue with the plasma glycolate assay at the testing laboratory the data for Part B could not be calculated.	
End point type	Secondary
End point timeframe:	
Part A (SAD phase): Baseline, Part B (MAD phase): Baseline	

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Plasma glycolate concentration was only calculated for Part A.

End point values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	6
Units: umol/L				
arithmetic mean (standard deviation)	5.1 (± 1.73)	5.3 (± 1.51)	5.7 (± 1.97)	6.2 (± 2.56)

End point values	Part A: SAD: Lumasiran 6.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: umol/L				
arithmetic mean (standard deviation)	4.8 (± 1.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Plasma Glycolate Concentration

End point title	Percentage Change from Baseline in Plasma Glycolate Concentration ^[9]
-----------------	--

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. Due to a quality issue with the plasma glycolate assay at the testing laboratory the data for Part B could not be calculated. In each row header within the table n indicates the number of subjects analysed for the specific time point.

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

End point timeframe:

Part A (SAD phase): Days 15, 29, 57 and 85; Part B (MAD phase): Days 15, 29, 57, 85

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Plasma glycolate concentration was only calculated for Part A.

End point values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	6
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 15 (n=8,6,6,6,6)	18.3 (± 67.19)	58.3 (± 55.29)	48.5 (± 82.99)	56.4 (± 28.50)
Day 29 (n=8,6,6,6,6)	22.4 (± 46.83)	32.9 (± 57.67)	70.6 (± 82.74)	146.4 (± 81.99)
Day 57 (n=8,6,6,6,6)	126.7 (± 242.68)	66.3 (± 38.07)	109.8 (± 124.29)	230.1 (± 180.36)
Day 85 (n=8,6,6,5,6)	31.2 (± 131.04)	15.6 (± 100.54)	40.7 (± 110.75)	196.2 (± 152.41)

End point values	Part A: SAD: Lumasiran 6.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 15 (n=8,6,6,6,6)	59.5 (± 49.00)			
Day 29 (n=8,6,6,6,6)	390.1 (± 270.40)			
Day 57 (n=8,6,6,6,6)	730.4 (± 439.54)			
Day 85 (n=8,6,6,5,6)	731.3 (± 375.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Spot Urine Glycolate:Creatinine Ratio in Part A

End point title	Baseline Spot Urine Glycolate:Creatinine Ratio in Part A ^[10]
-----------------	--

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments.

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

End point timeframe:

Part A (SAD phase): Baseline

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part A.

End point values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	6
Units: mg/g				
arithmetic mean (standard deviation)	12.4 (± 4.63)	15.7 (± 4.27)	15.7 (± 3.14)	13.0 (± 3.52)

End point values	Part A: SAD: Lumasiran 6.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			

Units: mg/g				
arithmetic mean (standard deviation)	14.8 (± 4.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Spot Urine Glycolate:Creatinine Ratio in Part A

End point title	Percentage Change from Baseline in Spot Urine Glycolate:Creatinine Ratio in Part A ^[11]
-----------------	--

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. In each row header within the table n indicates the number of subjects analysed for the specific time point.

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

End point timeframe:

Part A (SAD phase): Days 29 and 57

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part A.

End point values	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg	Part A: SAD: Lumasiran 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	6	6
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 29 (=8,6,6,6,6)	8.1 (± 43.42)	32.5 (± 22.6)	82.9 (± 65.00)	109.1 (± 66.51)
Day 57 (n=8,6,6,6,6)	73.8 (± 108.9)	38.0 (± 50.62)	47.8 (± 41.03)	215.0 (± 178.72)

End point values	Part A: SAD: Lumasiran 6.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 29 (=8,6,6,6,6)	210.5 (± 199.30)			
Day 57 (n=8,6,6,6,6)	310.7 (± 94.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline of 24 Hour Urine Oxalate Corrected for BSA in Part B

End point title	Baseline of 24 Hour Urine Oxalate Corrected for BSA in Part
-----------------	---

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments.

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

End point timeframe:

Part B (MAD): Baseline

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	8	8	4
Units: mmol/24h/1.73m ²				
arithmetic mean (standard deviation)	1.96 (± 0.321)	1.73 (± 0.696)	1.84 (± 0.621)	1.30 (± 0.350)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of 24 Hour Urine Oxalate Corrected for BSA in Part B

End point title	Percentage Change from Baseline of 24 Hour Urine Oxalate Corrected for BSA in Part B ^[13]
-----------------	--

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. In each row header within the table n indicates the number of subjects analysed for the specific time point. 9999 = Not Applicable as data for the Part B placebo arm were only collected up to Day 85. 99999 = SD was not calculated for arms with data for 1 subject.

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

End point timeframe:

Part B (MAD): 24 hour urine collections on Days 29, 57, 85, 113, 141, 169, 197

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	8	8	4
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 29 (n=1,7,7,4)	-2.4 (± 99999)	-41.1 (± 24.76)	-57.5 (± 10.84)	-49.2 (± 5.40)
Day 57 (n=2,7,8,4)	-27.8 (± 47.11)	-49.7 (± 20.08)	-72.5 (± 10.70)	-49.1 (± 5.82)
Day 85 (n=1,8,7,3)	9.1 (± 99999)	-65.6 (± 16.64)	-68.4 (± 10.60)	-53.3 (± 3.66)
Day 113 (n=0,7,6,4)	9999 (± 9999)	-61.4 (± 12.24)	-78.1 (± 7.80)	-59.1 (± 20.75)
Day 141 (n=0,7,7,2)	9999 (± 9999)	-64.6 (± 13.55)	-73.5 (± 8.11)	-68.4 (± 3.21)
Day 169 (n=0,8,7,3)	9999 (± 9999)	-61.6 (± 14.19)	-69.3 (± 9.61)	-48.7 (± 14.19)
Day 197 (n=0,6,7,4)	9999 (± 9999)	-63.8 (± 13.85)	-71.2 (± 11.70)	-52.7 (± 6.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline 24 Hour Urine Glycolate:Creatinine Ratio in Part B - Initial 85 Days

End point title	Baseline 24 Hour Urine Glycolate:Creatinine Ratio in Part B - Initial 85 Days ^[14]
-----------------	---

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments.

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

End point timeframe:

Part B (MAD): Baseline

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	7	7	3
Units: mg/g				
arithmetic mean (standard deviation)	193 (± 117.2)	241 (± 85.6)	289 (± 146.0)	281 (± 139.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of 24 Hour Urine Glycolate:Creatinine Ratio in Part B - Initial 85 Days

End point title	Percentage Change from Baseline of 24 Hour Urine Glycolate:Creatinine Ratio in Part B - Initial 85 Days ^[15]
-----------------	---

End point description:

PD Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. In each row header within the table n indicates the number of subjects analysed for the specific time point.

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

End point timeframe:

Part B (MAD): 24 hour urine collections on Days 29, 57 and 85.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	7	7	3
Units: percentage change from baseline				
arithmetic mean (standard deviation)				
Day 29 (n=3,7,7,3)	-15.1 (± 6.47)	53.1 (± 42.18)	31.4 (± 35.99)	33.0 (± 36.37)
Day 57 (n=3,7,7,3)	-13.8 (± 29.02)	82.3 (± 40.12)	42.3 (± 57.56)	81.8 (± 35.66)
Day 85 (n=3,7,7,2)	-23.0 (± 10.45)	71.0 (± 55.62)	43.7 (± 62.15)	42.0 (± 20.86)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Creatinine Clearance Corrected for BSA in Part B

End point title	Baseline Creatinine Clearance Corrected for BSA in Part B ^[16]
End point description: PD Analysis Set in Part B consisted of all patients with PH1 who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments.	
End point type	Secondary
End point timeframe: Part B (MAD): Baseline	

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	8	8	4
Units: mL/min/1.73 m ²				
arithmetic mean (standard deviation)	64.389 (± 19.8024)	108.149 (± 44.1783)	86.268 (± 22.1226)	88.251 (± 30.0118)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline of Creatinine Clearance Corrected for BSA in Part B

End point title	Percentage Change From Baseline of Creatinine Clearance Corrected for BSA in Part B ^[17]
End point description: PD Analysis Set in Part B consisted of all patients with PH1 who received at least 1 dose of study drug (lumasiran, placebo) and had at least 1 postdose blood and/or urine sample available that was evaluable for PD assessments. 9999 = Not Applicable as zero subjects were evaluated for this time point. 99999 = SD was not calculated for arms with data for 1 subject.	
End point type	Secondary
End point timeframe: Part B (MAD): Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449	

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was only measured in Part B.

End point values	Part B: MAD: Placebo	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg once every 3 months (q3M)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	8	8	4
Units: percentage change from baseline arithmetic mean (standard deviation)				
Day 29 (n=1,7,7,4)	9.019 (± 99999)	-6.672 (± 11.9614)	-0.624 (± 15.1771)	2.748 (± 5.6858)
Day 57 (n=2,7,8,4)	20.184 (± 23.5572)	-8.426 (± 19.7271)	4.505 (± 35.2457)	37.030 (± 56.1210)
Day 85 (n=1,8,7,2)	-5.945 (± 99999)	-13.536 (± 22.8679)	-3.720 (± 22.6231)	-6.113 (± 43.5441)
Day 113 (n=0,7,6,4)	9999 (± 9999)	-14.424 (± 24.1107)	3.444 (± 29.6749)	7.570 (± 40.5928)
Day 141 (n=0,7,7,2)	9999 (± 9999)	-8.804 (± 27.4802)	9.315 (± 27.5044)	-30.691 (± 12.8912)
Day 169 (n=0,8,7,1)	9999 (± 9999)	-19.796 (± 31.7492)	-8.544 (± 14.8481)	20.210 (± 99999)
Day 197 (n=0,6,7,4)	9999 (± 9999)	-8.546 (± 13.5672)	-13.513 (± 25.0560)	28.857 (± 22.1891)
Day 225 (n=0,6,8,3)	9999 (± 9999)	-18.221 (± 14.2322)	29.013 (± 53.5563)	-14.964 (± 9.9130)
Day 253 (n=0,6,7,0)	9999 (± 9999)	-5.140 (± 19.2839)	10.232 (± 24.4929)	9999 (± 9999)
Day 281 (n=0,6,6,0)	9999 (± 9999)	-14.283 (± 22.6126)	5.841 (± 13.0381)	9999 (± 9999)
Day 309 (n=0,5,4,0)	9999 (± 9999)	-0.403 (± 34.6839)	8.441 (± 11.5329)	9999 (± 9999)
Day 337 (n=0,4,4,0)	9999 (± 9999)	-5.168 (± 31.0756)	8.688 (± 24.2094)	9999 (± 9999)
Day 365 (n=0,2,2,0)	9999 (± 9999)	2.268 (± 33.7565)	9.201 (± 14.4856)	9999 (± 9999)
Day 393 (n=0,3,2,0)	9999 (± 9999)	-11.942 (± 45.3027)	-4.484 (± 12.6320)	9999 (± 9999)
Day 421 (n=0,3,2,0)	9999 (± 9999)	7.610 (± 11.2195)	-6.498 (± 12.9022)	9999 (± 9999)
Day 449 (n=0,0,2,0)	9999 (± 9999)	9999 (± 9999)	-15.093 (± 10.3705)	9999 (± 9999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A (SAD phase): Up to 405 days; Part B (MAD phase): Up to 546 days

Adverse event reporting additional description:

Safety Analysis Set consisted of all healthy subjects and patients who received at least 1 dose of study drug (lumasiran, placebo), grouped according to actual treatment received.

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

Dictionary used

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

Dictionary version	18.1
--------------------	------

Reporting groups

Reporting group title	Part A: SAD: Placebo
-----------------------	----------------------

Reporting group description:

A single dose of matching placebo was administered.

Reporting group title	Part A: SAD: Lumasiran 0.3 mg/kg
-----------------------	----------------------------------

Reporting group description:

A single dose of 0.3 mg/kg lumasiran was administered.

Reporting group title	Part A: SAD: Lumasiran 1.0 mg/kg
-----------------------	----------------------------------

Reporting group description:

A single dose of 1.0 mg/kg lumasiran was administered.

Reporting group title	Part A: SAD: Lumasiran 3.0 mg/kg
-----------------------	----------------------------------

Reporting group description:

A single dose of 3.0 mg/kg lumasiran was administered.

Reporting group title	Part A: SAD: Lumasiran 6.0 mg/kg
-----------------------	----------------------------------

Reporting group description:

A single dose of 6.0 mg/kg lumasiran was administered.

Reporting group title	Part B: MAD: Placebo
-----------------------	----------------------

Reporting group description:

Subjects with PH1 were treated with placebo matching one of the lumasiran dosages (one placebo subject for each lumasiran arm). After 85 days these subjects crossed over to the lumasiran groups.

Reporting group title	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)
-----------------------	--

Reporting group description:

Subjects with PH1 were treated with 1.0 mg/kg lumasiran qM for 197 days.

Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg qM
-----------------------	-------------------------------------

Reporting group description:

Subjects with PH1 were treated with 3.0 mg/kg lumasiran qM for 197 days.

Reporting group title	Part B: MAD: Lumasiran 3.0 mg/kg q3M
-----------------------	--------------------------------------

Reporting group description:

Subjects with PH1 were treated with 3.0 mg/kg lumasiran q3M for 197 days.

Serious adverse events	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg q3M
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part A: SAD: Placebo	Part A: SAD: Lumasiran 0.3 mg/kg	Part A: SAD: Lumasiran 1.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	6 / 6 (100.00%)	3 / 6 (50.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site discolouration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Social circumstances			

Caffeine consumption subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Psychiatric disorders			
Alcoholic hangover subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 6 (16.67%) 3	0 / 6 (0.00%) 0
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tendon injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Soft tissue injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tricuspid valve incompetence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Lethargy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood and lymphatic system disorders Lymph node pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Eye disorders Dry eye subjects affected / exposed occurrences (all) Eye swelling subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Faeces soft subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0	1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0

subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash follicular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin texture abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysuria			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	3 / 8 (37.50%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Periodontitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Body tinea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis infected			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Overweight			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part A: SAD: Lumasiran 3.0 mg/kg	Part A: SAD: Lumasiran 6.0 mg/kg	Part B: MAD: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	2 / 3 (66.67%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	4 / 6 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Axillary pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site discolouration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Injection site swelling subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Social circumstances Caffeine consumption subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Nasal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Psychiatric disorders Alcoholic hangover subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Blood creatine phosphokinase increased			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 3 (33.33%) 1
Head injury subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	0 / 3 (0.00%) 0
Tendon injury subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Soft tissue injury subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Congenital, familial and genetic disorders			
Atrial septal defect subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Cardiac disorders			
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	3 / 6 (50.00%) 3	0 / 3 (0.00%) 0

Presyncope subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 3 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Blood and lymphatic system disorders Lymph node pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Eye disorders Dry eye subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Visual impairment subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Faeces soft subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0
Flatulence			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Teething			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash follicular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin texture abnormal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	0 / 3 (0.00%)
occurrences (all)	4	4	0
Periodontitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Viral pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Body tinea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis infected			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Overweight			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: MAD: Lumasiran 1.0 mg/kg once monthly (qM)	Part B: MAD: Lumasiran 3.0 mg/kg qM	Part B: MAD: Lumasiran 3.0 mg/kg q3M
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	7 / 8 (87.50%)	4 / 4 (100.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Axillary pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injection site bruising			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injection site discolouration			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Injection site pruritus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Injection site swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	0 / 4 (0.00%) 0
Social circumstances Caffeine consumption subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Nasal discomfort subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2	2 / 8 (25.00%) 2	0 / 4 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 4 (25.00%) 1
Psychiatric disorders Alcoholic hangover subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tendon injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Soft tissue injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	2 / 8 (25.00%) 7	0 / 4 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	0 / 4 (0.00%) 0
Blood and lymphatic system disorders			
Lymph node pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Visual impairment subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 2	0 / 4 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	3 / 8 (37.50%) 3	1 / 4 (25.00%) 1

Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Faeces soft			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Teething			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash follicular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin texture abnormal			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Blister subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 8 (37.50%) 3	0 / 4 (0.00%) 0
Dysuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Groin pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0
Influenza			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Periodontitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dermatitis infected			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	3 / 8 (37.50%)	0 / 4 (0.00%)
occurrences (all)	1	4	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection enterococcal			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	5
Overweight			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2016	1. Provided starting dose of lumasiran (1.0 mg/kg) for SC administration every 28 days to PH1 patients in Part B, based on preliminary data from Part A in healthy volunteers. 2. Added cohort progression/escalation and suspension/stopping rules pertaining to AEs. For Part B only, 3. Clarified details regarding collection and evaluation of urinary oxalate and glycolate measurements. 4. Specified that on days when a blood sample for vitamin B6 should be collected, patients should be instructed to not take vitamin B6 before the blood sample is collected and the study drug is administered. 5. Removed 28-day window from the schedule of assessment for the Day 85 study visit to indicate that this visit must occur on the scheduled day. 6. Clarified that additional cohorts may be enrolled at higher, lower, or intermediate dose levels, but will not exceed the maximum administered dose of 6.0 mg/kg. For Parts A and B, 7. Specified that plasma samples, in addition to urine samples, are collected for assessment of pharmacodynamic (PD) assessments.
21 September 2016	1. For Parts A and B, subjects were to be followed until PD recovery occurred (until plasma glycolate decreased to a level that was no more than 20% above baseline or until plasma glycolate was below upper limit of normal (ULN ≤ 14 micromol/L). 2. For Part B, subjects with PH1 were to be followed until urinary oxalate increased to a level above 80% of baseline. 3. For Part B, blood samples for anti-drug antibodies (ADA) analysis were added at final dosing/end of treatment (EOT) visit, at 28 days after final lumasiran dose, and every 56 days for remainder of follow-up periods. 4. Language added to indicate confirmed positive ADA samples are tested for cross-reactivity with DNA and nucleic acids. 5. For Part B, pharmacokinetic (PK) sampling times adjusted to capture full PK profile and relieve burden on subject. Clinic visits added at Day 3, Day 58, and Day 59, accordingly. For subjects initially receiving placebo, clinic visits added at Day 87, Day 142, and Day 143. 6. Clarified that liver function tests (LFTs) would be reviewed locally and confirmed by central laboratory prior to study drug administration.
09 December 2016	1. To further define cardiac function requirements and monitoring for all Part B subjects, based on safety review committee (SRC) recommendations. 2. Added echocardiogram (ECG) and troponin I assessments and exclusion criterion of left ventricular ejection fraction $<55\%$ and troponin I $>ULN$ at screening. 3. Increased maximum blood volume to align with cardiac monitoring evaluations. 4. Aligned wording describing resumption of dosing requirements after dose suspension rule had been met.

27 June 2017	1. Shortened the Part B follow-up period so that subjects could transition to open-label extension study earlier, provided that urinary oxalate was >ULN and subjects met at least 1 specific PD recovery criterion: - o One 24-hour urinary oxalate value was >80% of baseline. - o Two 24-hour urinary oxalate values above the midpoint between baseline and nadir 24-hour urinary oxalate values. - o At least 12 months from time of final dose. 2. Increased the number of optional cohorts and sample size in Part B in order to further explore optimal dose. 3. Schedule of Assessments to allow for once every 3 months dosing in Part B was added. 4. Statistical Methods section updated to account for possibility of once every 3 months dosing regimen. 5. Section about the SRC aligned with recent changes to SRC charter regarding frequency of safety data reviews.
14 February 2018	1. Extended the allowable time window (from 1 to 2 hours) to conduct predose assessments (i.e., vital signs, 12-lead ECGs, physical examinations, blood and urine sample collections) when scheduled at the same time points for Part B. 2. Shortened the follow-up period from up to 1 year to 12 weeks after final lumasiran dose, without requiring protocol-defined thresholds for urinary oxalate levels for subjects who planned to enroll in the extension study for continued dosing. 3. Added new text to permit the Investigator, following completion of the 12-week follow-up period and per SRC approval, to discontinue safety and PD follow-up for subjects who did not enroll in the open-label extension study, and who had not yet met the PD recovery criteria. 4. Redefined the definition for uncontrolled hypertension in paediatric patients. 5. Clarified that blood samples for pyridoxine (vitamin B6) were required only for subjects receiving therapeutic pyridoxine.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 October 2016	The study was temporarily halted, with a pause in start of enrollment of patients for Part B of the study. This was to allow a recommendation from a scheduled Safety Review Committee to be incorporated in the protocol, at which point study screening resumed	15 December 2016

Notes:

Limitations and caveats

None reported