



Clinical trial results:

ILLUMINATE-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Summary

EudraCT number	2018-001981-40
Trial protocol	GB FR DE NL
Global end of trial date	12 January 2024

Results information

Result version number	v1 (current)
This version publication date	28 July 2024
First version publication date	28 July 2024

Trial information

Trial identification

Sponsor protocol code	ALN-GO1-003
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03681184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, United States, 02142
Public contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., 001 877256 9526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., 001 877256 9526, clinicaltrials@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	12 January 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of lumasiran in children and adults with primary hyperoxaluria type 1 (PH1).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Arab Emirates: 1
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	39
EEA total number of subjects	10

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)	16
Adolescents (12-17 years)	6
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with PH1 were enrolled at sixteen sites in France, Germany, Israel, the Netherlands, Switzerland, the United Arab Emirates, the United Kingdom and the United States.

Pre-assignment

Screening details:

Subjects were treated with placebo or lumasiran during the 6-month Double-Blind Period. All subjects received lumasiran during the 3-Month Blinded Treatment Extension Period and 51-Month Open-Label Extension Period.

Period 1

Period 1 title	6-Month Double-Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Lumasiran

Arm description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

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

Dosage and administration details:

Placebo by SC injection

Arm title	Lumasiran/Lumasiran
------------------	---------------------

Arm description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

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 by SC injection

Number of subjects in period 1	Placebo/Lumasiran	Lumasiran/Lumasiran
Started	13	26
Completed	13	25
Not completed	0	1
Parent/Caregiver Withdrew Consent	-	1

Period 2

Period 2 title	3-Month Blinded Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Lumasiran

Arm description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

Arm type	Placebo
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 by SC injection

Arm title	Lumasiran/Lumasiran
------------------	---------------------

Arm description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

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 by SC injection

Number of subjects in period 2 ^[1]	Placebo/Lumasiran	Lumasiran/Lumasiran
Started	13	24
Completed	13	24

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 1 subject discontinued study drug and entered safety follow up after the DB period.

Period 3

Period 3 title	Open-Label Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Lumasiran

Arm description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

Arm type	Placebo
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 by SC injection

Arm title	Lumasiran/Lumasiran
------------------	---------------------

Arm description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

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 by SC injection

Number of subjects in period 3	Placebo/Lumasiran	Lumasiran/Lumasiran
Started	13	24
Completed	13	24

Baseline characteristics

Reporting groups

Reporting group title	Placebo/Lumasiran
Reporting group description:	
Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.	
Reporting group title	Lumasiran/Lumasiran
Reporting group description:	
Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.	

Reporting group values	Placebo/Lumasiran	Lumasiran/Lumasiran	Total
Number of subjects	13	26	39
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	17.0	18.7	-
standard deviation	± 15.19	± 11.52	-
Gender categorical Units: Subjects			
Female	5	8	13
Male	8	18	26
24-Hour Urinary Oxalate Excretion Corrected for BSA Units: mmol/24hr/1.73m ²			
arithmetic mean	1.7994	1.836	-
standard deviation	± 0.6836	± 0.5966	-
Estimated Glomerular Filtration Rate (eGFR) Units: mL/min/1.73m ²			
arithmetic mean	78.834	82.967	-
standard deviation	± 29.9841	± 25.5499	-
24-hour Urinary Oxalate:Creatinine Ratio Units: mmol/mmol			
arithmetic mean	0.231	0.209	-
standard deviation	± 0.1306	± 0.1012	-

End points

End points reporting groups

Reporting group title	Placebo/Lumasiran
-----------------------	-------------------

Reporting group description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

Reporting group title	Lumasiran/Lumasiran
-----------------------	---------------------

Reporting group description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

Reporting group title	Placebo/Lumasiran
-----------------------	-------------------

Reporting group description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

Reporting group title	Lumasiran/Lumasiran
-----------------------	---------------------

Reporting group description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

Reporting group title	Placebo/Lumasiran
-----------------------	-------------------

Reporting group description:

Lumasiran-matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC) at Day 1 and Months 1, 2 and 3 during the 6-Month Double-blind (DB) Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month Open-label Extension (OLE) period.

Reporting group title	Lumasiran/Lumasiran
-----------------------	---------------------

Reporting group description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

Subject analysis set title	DB Period: Placebo
----------------------------	--------------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

Lumasiran-matching placebo was administered SC at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period.

Primary: Percent Change in 24-hour Urinary Oxalate Excretion Corrected for Body Surface Area (BSA) From Baseline to Month 6

End point title	Percent Change in 24-hour Urinary Oxalate Excretion Corrected for Body Surface Area (BSA) From Baseline to Month 6
-----------------	--

End point description:

Percent change in 24-hour urinary oxalate excretion corrected for BSA was estimated by an average percent change from baseline across Months 3 through 6. Only valid urine samples without any non-protocol-related issues were included in the analysis. A negative change from Baseline indicates a favorable outcome. Full Analysis Set (FAS): All randomized subjects who received any amount of study drug.

End point type	Primary
End point timeframe:	
Baseline to Month 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: percent change				
least squares mean (standard error)	-11.8 (± 3.8)	-65.4 (± 2.9)		

Statistical analyses

Statistical analysis title	Percent Change in 24-hour urinary oxalate
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001 ^[2]
Method	[MMRM]
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-53.546
Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.314
upper limit	-44.778
Variability estimate	Standard error of the mean
Dispersion value	4.3224

Notes:

[1] - The Mixed-Effect Model Repeated Measures (MMRM) includes fixed effects of treatment arms (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5, and 6), baseline 24-hour urinary oxalate corrected for BSA as a continuous fixed covariate, and subject as a random effect. The variance-covariance matrix is assumed to be unstructured. Satterthwaite approximation is used to estimate denominator degrees of freedom.

[2] - P=1.685E-14

Secondary: Absolute Change in 24-hour Urinary Oxalate Corrected for BSA From Baseline to Month 6

End point title	Absolute Change in 24-hour Urinary Oxalate Corrected for BSA From Baseline to Month 6
-----------------	---

End point description:

Absolute change in 24-hour urinary oxalate excretion corrected for BSA was estimated by an average absolute change from baseline across Months 3 through 6. Only valid urine samples without any non-protocol-related issues were included in the analysis. A negative change from Baseline indicates a favorable outcome. FAS includes all randomized subjects who received any amount of study drug.

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

End point timeframe:

Baseline to Month 6

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: mmol/24hr/1.73m ²				
least squares mean (standard error)	-0.27 (± 0.08)	-1.24 (± 0.06)		

Statistical analyses

Statistical analysis title	Absolute Change in 24-hour Urinary Oxalate
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001 ^[4]
Method	[MMRM]
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-0.975
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.177
upper limit	-0.772
Variability estimate	Standard error of the mean
Dispersion value	0.0998

Notes:

[3] - The MMRM includes fixed effects of treatment arms (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5, and 6), baseline 24-hour urinary oxalate corrected for BSA as a continuous fixed covariate, and subject as a random effect. The variance-covariance matrix is assumed to be unstructured. Satterthwaite approximation is used to estimate denominator degrees of freedom.

[4] - P=1.225E-11

Secondary: Percent Change in 24-hour Urinary Oxalate:Creatinine Ratio From Baseline to Month 6

End point title	Percent Change in 24-hour Urinary Oxalate:Creatinine Ratio From Baseline to Month 6
End point description:	Percent change in 24-hour urinary oxalate:creatinine ratio was estimated by an average percent change from baseline across Months 3 through 6. A negative change from Baseline indicates a favorable outcome. FAS: All randomized subjects who received any amount of study drug.
End point type	Secondary
End point timeframe:	
Baseline to Month 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: percent change				
least squares mean (standard error)	-10.8 (± 5.4)	-62.5 (± 4.0)		

Statistical analyses

Statistical analysis title	Percent Change
Statistical analysis description:	
Percent Change in 24-hour Urinary Oxalate:Creatinine Ratio From Baseline to Month 6	
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001 ^[6]
Method	[MMRM]
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-51.7718
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.2653
upper limit	-39.2784
Variability estimate	Standard error of the mean
Dispersion value	6.16118

Notes:

[5] - The MMRM includes fixed effects of treatment arms (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5, and 6), baseline 24-hour urinary oxalate:creatinine ratio as a continuous fixed covariate, and subject as a random effect. The variance-covariance matrix is assumed to be unstructured. Satterthwaite approximation is used to estimate denominator degrees of freedom.

[6] - P=5.032E-10

Secondary: Percentage of Subjects With 24-hour Urinary Oxalate Level Corrected for BSA at or Below 1.5 x ULN at Month 6

End point title	Percentage of Subjects With 24-hour Urinary Oxalate Level Corrected for BSA at or Below 1.5 x ULN at Month 6
End point description:	
The upper limit of normal (ULN) = 0.514 mmol/24hr/1.73m ² for 24-hour urinary oxalate excretion corrected for BSA. Subjects from the FAS (all randomized subjects who received any amount of study drug) for whom data are available. Number analysed is the number of subjects with data available for analysis.	
End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: percentage of subjects				
number (not applicable)	0	84.0		

Statistical analyses

Statistical analysis title	Percentage of Subjects
Statistical analysis description:	
The proportion of subjects (lumasiran vs. placebo) with 24-hour urinary oxalate $\leq 1.5 \times \text{ULN}$ at Month 6 is analyzed using the Cochran–Mantel–Haenszel test, stratified by baseline 24-hour urinary oxalate corrected for BSA ($\leq 1.70 \text{ mmol/24hr/1.73m}^2$ vs. $> 1.70 \text{ mmol/24hr/1.73m}^2$). The difference in proportion (lumasiran vs. placebo) and the corresponding 95% confidence interval are calculated using the Newcombe method, based on the Wilson score.	
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.94

Notes:

[7] - $P=8.341\text{E-}07$

Secondary: Percentage of Subjects With 24-hour Urinary Oxalate Level Corrected for BSA at or Below ULN at Month 6

End point title	Percentage of Subjects With 24-hour Urinary Oxalate Level Corrected for BSA at or Below ULN at Month 6
End point description:	
The upper limit of normal (ULN) = $0.514 \text{ mmol/24hr/1.73m}^2$ for 24-hour urinary oxalate excretion corrected for BSA.	
Subjects from the FAS (all randomized subjects who received any amount of study drug) for whom data are available. Number analysed is the number of subjects with data available for analysis.	
End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: percentage of subjects				
number (not applicable)	0	52.0		

Statistical analyses

Statistical analysis title	Percentage of Subjects
Statistical analysis description:	
The proportion of subjects (lumasiran vs. placebo) with 24-hour urinary oxalate \leq ULN at Month 6 is analyzed using the Cochran–Mantel–Haenszel test, stratified by baseline 24-hour urinary oxalate corrected for BSA (≤ 1.70 mmol/24hr/1.73m ² vs. > 1.70 mmol/24hr/1.73m ²). The difference in proportion (lumasiran vs. placebo) and the corresponding 95% confidence interval are calculated using the Newcombe method, based on the Wilson score.	
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.7

Secondary: Percentage Change in Plasma Oxalate From Baseline to Month 6

End point title	Percentage Change in Plasma Oxalate From Baseline to Month 6
End point description:	
Percent change in plasma oxalate (umol/L) was estimated by an average percent change from baseline across Months 3 through 6. A negative change from Baseline indicates a favorable outcome. Plasma Oxalate Analysis Set: all subjects who received any amount of study drug and had baseline plasma oxalate level ≥ 1.5 times lower limit of quantitation (LLOQ). LLOQ is 5.55 mcg/L. Number analysed is the number of subjects with data available for analysis.	
End point type	Secondary
End point timeframe:	
Baseline to Month 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	23		
Units: percent change				
least squares mean (standard error)	-0.3 (± 4.3)	-39.8 (± 2.9)		

Statistical analyses

Statistical analysis title	Percentage Change in Plasma Oxalate
----------------------------	-------------------------------------

Statistical analysis description:

The MMRM includes fixed effects of treatment arms (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5, and 6), baseline plasma oxalate as a continuous fixed covariate, and subject as a random effect. The variance-covariance matrix is assumed to be unstructured. Satterthwaite approximation is used to estimate denominator degrees of freedom.

Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	[MMRM]
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-39.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.1
upper limit	-28.87
Variability estimate	Standard error of the mean
Dispersion value	5.181

Notes:

[8] - P=2.862E-08

Secondary: Absolute Change in Plasma Oxalate From Baseline to Month 6

End point title	Absolute Change in Plasma Oxalate From Baseline to Month 6
-----------------	--

End point description:

Absolute change in plasma oxalate (umol/L) was estimated by an average percent change from baseline across Months 3 through 6. A negative change from Baseline indicates a favorable outcome. Plasma Oxalate Analysis Set: all subjects who received any amount of study drug and had baseline plasma oxalate level ≥ 1.5 times lower limit of quantitation (LLOQ). LLOQ is 5.55 mcg/L. Number analysed is the number of subjects with data available for analysis.

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

End point timeframe:

Baseline to Month 6

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	23		
Units: µmol/L				
least squares mean (standard error)	1.3 (± 1.1)	-7.5 (± 0.8)		

Statistical analyses

Statistical analysis title	Absolute Change in Plasma Oxalate
Comparison groups	Placebo/Lumasiran v Lumasiran/Lumasiran
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.0001 ^[10]
Method	[MMRM]
Parameter estimate	Difference in Least Squares (LS) Mean
Point estimate	-8.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.45
upper limit	-5.98
Variability estimate	Standard error of the mean
Dispersion value	1.338

Notes:

[9] - The MMRM includes fixed effects of treatment arms (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5, and 6), baseline plasma oxalate as a continuous fixed covariate, and subject as a random effect. The variance-covariance matrix is assumed to be unstructured. Satterthwaite approximation is used to estimate denominator degrees of freedom.

[10] - P=3.893E-07

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline to Week 2 and Months 1, 2, 3, 4, 5 and 6

End point title	Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline to Week 2 and Months 1, 2, 3, 4, 5 and 6
-----------------	--

End point description:

eGFR is calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients >1 year to <18 years of age at screening. Change from baseline to Month 6 is reported. Subjects from the FAS (all randomized subjects who received any amount of study drug) for whom data are available. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
End point timeframe:	
Baseline, Week 2, Months 1, 2, 3, 4, 5 and 6	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	25		
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)				
Week 2 (n= 13, 24)	-5 (± 9)	-4 (± 9)		
Month 1 (n= 12, 25)	-6 (± 7)	-2 (± 12)		
Month 2 (n= 13, 25)	-5 (± 8)	-2 (± 15)		
Month 3 (n= 13, 25)	-3 (± 6)	0 (± 11)		
Month 4 (n= 12, 25)	-4 (± 8)	-4 (± 10)		
Month 5 (n= 13, 25)	-4 (± 7)	-6 (± 13)		
Month 6 (n= 13, 25)	0 (± 6)	-3 (± 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in 24-hour Urinary Oxalate Excretion Corrected for BSA From Baseline in the Extension Period

End point title	Absolute Change in 24-hour Urinary Oxalate Excretion Corrected for BSA From Baseline in the Extension Period
-----------------	--

End point description:

Absolute change in 24-hour urinary oxalate excretion corrected for BSA was estimated by an average absolute change from baseline in the extension periods. Only valid urine samples without any non-protocol-related issues were included in the analysis. A negative change from Baseline indicates a favorable outcome.

All Lumasiran Treated Set: All subjects who received any amount of lumasiran including subjects who took lumasiran during the 6-month double-blinded period and subjects who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period. 999 indicates that data was not evaluable at given time point. Number analysed is the number of subjects with data available for analysis.

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

End point timeframe:

From Baseline to Month 54 and Month 60

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	23		
Units: mmol/24hr/1.73m ²				
arithmetic mean (standard deviation)				
At Month 54 (n= 6, 23)	-0.951 (± 0.6148)	-1.086 (± 0.7678)		
At Month 60 (n= 0, 19)	9999 (± 9999)	-1.129 (± 0.7581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in 24-hour Urinary Oxalate Excretion Corrected by BSA From Baseline in the Extension Period

End point title	Percentage Change in 24-hour Urinary Oxalate Excretion Corrected by BSA From Baseline in the Extension Period
-----------------	---

End point description:

Percent change in 24-hour urinary oxalate excretion corrected for BSA was estimated by an average percent change from baseline in the extension periods. Only valid urine samples without any non-protocol-related issues were included in the analysis.

All Lumasiran Treated Set: All subjects who received any amount of lumasiran including subjects who took lumasiran during the 6-month double-blinded period and subjects who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period. A negative change from Baseline indicates a favorable outcome. 999 indicates that data was not evaluable at given time point. Number analysed is the number of subjects with data available for analysis.

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

End point timeframe:

From Baseline to Month 54 and Month 60

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	23		
Units: percent change				
arithmetic mean (standard deviation)				
At Month 54 (n= 6, 23)	-55.57 (± 11.903)	-53.87 (± 41.919)		
At Month 60 (n= 0, 19)	9999 (± 9999)	-53.98 (± 28.476)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Time That 24-hour Urinary Oxalate is at or Below 1.5 × ULN During Lumasiran Treatment

End point title	Percentage of Time That 24-hour Urinary Oxalate is at or Below 1.5 × ULN During Lumasiran Treatment
-----------------	---

End point description:

The upper limit of normal (ULN) = 0.514 mmol/24hr/1.73m² for 24-hour urinary oxalate excretion corrected for BSA.

All Lumasiran Treated Set: All subjects who received any amount of lumasiran including subjects who took lumasiran during the 6-month double-blinded period and subjects who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period.

End point type	Secondary
End point timeframe:	
Up to Month 60	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: percentage of time				
median (full range (min-max))	89.44 (21.1 to 99.3)	89.23 (1.7 to 98.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in 24-hour Urinary Oxalate:Creatinine Ratio From Baseline in the Extension Period

End point title	Absolute Change in 24-hour Urinary Oxalate:Creatinine Ratio From Baseline in the Extension Period
-----------------	---

End point description:

Absolute change in 24-hour urinary oxalate:creatinine ratio was estimated by an average absolute change from baseline to the end of the OLE period at Month 54 and Month 60. A negative change from Baseline indicates a favorable outcome. All Lumasiran Treated Set: All subjects who received any amount of lumasiran including subjects who took lumasiran during the 6-month double-blinded period and subjects who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period. 999 indicates that data was not evaluable at given time point. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
End point timeframe:	
From Baseline to Month 54 and Month 60	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	24		
Units: mmol/mmol				
arithmetic mean (standard deviation)				
At Month 54 (n=6, 24)	-0.145 (± 0.1242)	-0.127 (± 0.1063)		
At Month 60 (n=0, 19)	9999 (± 9999)	-0.138 (± 0.1162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline in the Extension Period

End point title	Change in Estimated Glomerular Filtration Rate (eGFR) From Baseline in the Extension Period
-----------------	---

End point description:

eGFR is calculated from serum creatinine based on the Modification of Diet in Renal Disease formula for patients ≥ 18 years of age and the Schwartz Bedside Formula for patients >1 year to <18 years of age at screening. All Lumasiran Treated Set: All subjects who received any amount of lumasiran including subjects who took lumasiran during the 6-month double-blinded period and subjects who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period. 999 indicates that data was not evaluable at given time point. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
End point timeframe:	
From Baseline to Month 54 and Month 60	

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	23		
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)				
At Month 54 (n= 6,23)	-12.860 (\pm 9.5386)	-6.899 (\pm 12.9302)		
At Month 60 (n= 0, 18)	9999 (\pm 9999)	-2.892 (\pm 11.6544)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)
-----------------	---

End point description:

AE is any untoward medical occurrence in clinical investigational subject administered a medicinal product & which does not necessarily have a causal relationship with this treatment. SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient

hospitalization/prolongs existing hospitalization, results in persistent/significant disability/incapacity, is congenital anomaly/birth defect, is an important medical event that may not be immediately life-threatening or result in death/hospitalization but may jeopardize subject & may require intervention to prevent one of the outcomes listed above. Per the SAP, long-term safety of lumasiran was summarized by sequence (placebo/lumasiran & lumasiran/lumasiran) using the All Lumasiran Treated Set. In this set, data is presented during lumasiran treatment only. Lumasiran/Lumasiran: lumasiran administered in both DB & Extension Period (EP) hence, safety data is reported together for DB & EP.

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

End point timeframe:

DB Period (Placebo): From first dose of study drug (Day 1) up to Month 6; Placebo/Lumasiran: From first dose of lumasiran (Month 6) up to end of study (Month 60); Lumasiran/Lumasiran: From first dose of lumasiran (Day 1) up to end of study (Month 60).

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran	DB Period: Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	26	13	
Units: subjects				
number (not applicable)				
Adverse Event (AE)	12	25	9	
Serious Adverse Event (SAE)	1	5	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Rate of Renal Stone Events

End point title	Rate of Renal Stone Events
-----------------	----------------------------

End point description:

A renal stone event is defined as a subject-reported event that includes ≥ 1 of the following: visit to healthcare provider because of a renal stone; medication for renal colic; stone passage; macroscopic hematuria due to a renal stone. Lower rates indicate a favorable outcome. FAS: All randomized subjects who received any amount of study drug.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

12-Month Period prior to Informed Consent, 6-Month DB Period

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	26		
Units: rate per person-year				
number (confidence interval 95%)				
12-Month Period prior to Informed Consent	0.54 (0.26 to 1.13)	3.19 (2.57 to 3.96)		
6-Month DB Period	0.66 (0.25 to 1.76)	1.09 (0.63 to 1.87)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Nephrocalcinosis as Assessed by Renal Ultrasound

End point title	Change From Baseline in Nephrocalcinosis as Assessed by Renal Ultrasound
-----------------	--

End point description:

Renal ultrasound data were used to grade medullary nephrocalcinosis findings (range: 0 to 3), where a higher grade indicates greater severity. Improving=if both sides improve, or one side improves and the other side has no change; No change=if both sides have no change; Worsening=if both sides worsen, or one side worsens and the other side has no change; Indeterminate=if one side improves and the other side worsens. Subjects from the FAS (all randomized subjects who received any amount of study drug) with both Baseline and Month 6 renal ultrasounds.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Baseline, Month 6

End point values	Placebo/Lumasiran	Lumasiran/Lumasiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	22		
Units: subjects				
number (not applicable)				
Improving	0	3		
No Change	11	19		
Worsening	1	0		
Indeterminate	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Period (Placebo): From first dose of study drug (Day 1) up to Month 6; Placebo/Lumasiran: From first dose of lumasiran (Month 6) up to end of study (Month 60); Lumasiran/Lumasiran: From first dose of lumasiran (Day 1) up to end of study (Month 60).

Adverse event reporting additional description:

Per the SAP, long-term safety of lumasiran was summarized by sequence (placebo/lumasiran & lumasiran/lumasiran) using the All Lumasiran Treated Set. In this set, data is presented during lumasiran treatment only. Lumasiran/Lumasiran: lumasiran administered in both DB & Extension Period (EP) hence, safety data is reported together for DB & EP.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo/Lumasiran
-----------------------	-------------------

Reporting group description:

Lumasiran-matching placebo was administered SC at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg, at Months 6, 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

Reporting group title	Lumasiran/Lumasiran
-----------------------	---------------------

Reporting group description:

Lumasiran was administered SC, 3.0 mg/kg, at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period, followed by lumasiran SC, 3.0 mg/kg at Month 6, and lumasiran-matching placebo SC at Months 7 and 8 during the 3-Month Blinded Treatment Extension Period, followed by lumasiran SC, 3.0 mg/kg, at Month 9 and then every three months during the 51-Month OLE period.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Lumasiran-matching placebo was administered SC at Day 1 and Months 1, 2 and 3 during the 6-Month DB Period.

Serious adverse events	Placebo/Lumasiran	Lumasiran/Lumasiran	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	5 / 26 (19.23%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Follicular lymphoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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
Injury, poisoning and procedural complications			

Post procedural complication subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (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
Renal impairment subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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			
Post procedural infection subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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
Urinary tract infection subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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
Urosepsis subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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

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

Non-serious adverse events	Placebo/Lumasiran	Lumasiran/Lumasiran	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	25 / 26 (96.15%)	9 / 13 (69.23%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	4	0
White coat hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pregnancy, puerperium and perinatal conditions			
Post abortion haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Catheter site extravasation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	5	0
Influenza like illness			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Injection site discomfort			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	5	0
Injection site erythema			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 13 (0.00%)
occurrences (all)	1	10	0

Injection site pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 17	4 / 26 (15.38%) 37	0 / 13 (0.00%) 0
Injection site reaction subjects affected / exposed occurrences (all)	5 / 13 (38.46%) 17	9 / 26 (34.62%) 17	0 / 13 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 26 (0.00%) 0	0 / 13 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 5	3 / 26 (11.54%) 5	0 / 13 (0.00%) 0
Vaccination site pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	3 / 26 (11.54%) 4	0 / 13 (0.00%) 0
Vaccination site swelling subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Immunisation reaction subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 26 (7.69%) 6	0 / 13 (0.00%) 0
Milk allergy subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Reproductive system and breast disorders			
Ovarian cyst subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Priapism			

subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Testicular pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 13 (7.69%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Nasal congestion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	1 / 13 (7.69%)
occurrences (all)	2	3	1
Productive cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	5	0
Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Enuresis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Fear of injection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Irritability			

subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Separation anxiety disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Weight increased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nail injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	1 / 13 (7.69%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Skin abrasion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Sunburn			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tibia fracture			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 26 (3.85%) 0	0 / 13 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 26 (0.00%) 0	1 / 13 (7.69%) 1
Gastrostomy tube site complication subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 26 (0.00%) 0	1 / 13 (7.69%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 26 (0.00%) 0	1 / 13 (7.69%) 1
Congenital, familial and genetic disorders Thalassaemia beta subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Cardiac disorders Arrhythmia supraventricular subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 26 (0.00%) 0	0 / 13 (0.00%) 0
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 3	0 / 13 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 26 (7.69%) 7	0 / 13 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	5 / 26 (19.23%) 10	3 / 13 (23.08%) 3
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Migraine			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 26 (0.00%) 0	0 / 13 (0.00%) 0
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 2	0 / 13 (0.00%) 0
Dacryostenosis acquired subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	1 / 13 (7.69%) 1
Abdominal pain			

subjects affected / exposed	1 / 13 (7.69%)	8 / 26 (30.77%)	0 / 13 (0.00%)
occurrences (all)	6	14	0
Abdominal pain lower			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	4	2	0
Abdominal tenderness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gingival hypertrophy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	2	8	0
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	3	2	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Skin and subcutaneous tissue disorders			
Actinic cheilitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 13 (0.00%)
occurrences (all)	1	3	0
Dermatitis atopic			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Livedo reticularis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Rash erythematous			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin lesion			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 13 (0.00%)
occurrences (all)	11	10	0
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Hypertonic bladder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypocitraturia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Microalbuminuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Renal pain			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	0 / 13 (0.00%)
occurrences (all)	3	5	0

Urinary incontinence subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 26 (7.69%) 5	0 / 13 (0.00%) 0
Flank pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	3 / 26 (11.54%) 3	1 / 13 (7.69%) 1
Groin pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 26 (0.00%) 0	0 / 13 (0.00%) 0
Infections and infestations			
Asymptomatic COVID-19 subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 26 (3.85%) 1	0 / 13 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 7	4 / 26 (15.38%) 4	0 / 13 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 26 (0.00%) 0	0 / 13 (0.00%) 0
Ear infection			

subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Fungal foot infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Fungal skin infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Furuncle			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	2 / 13 (15.38%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Herpes simplex reactivation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infected bite			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)	4 / 26 (15.38%)	0 / 13 (0.00%)
occurrences (all)	2	7	0
Onychomycosis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 26 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Pyelitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	3	0
Pyelonephritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis acute			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	3 / 13 (23.08%)	2 / 26 (7.69%)	2 / 13 (15.38%)
occurrences (all)	5	6	2
Tonsillitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	3 / 26 (11.54%)	2 / 13 (15.38%)
occurrences (all)	1	3	2
Urinary tract infection			

subjects affected / exposed	0 / 13 (0.00%)	3 / 26 (11.54%)	0 / 13 (0.00%)
occurrences (all)	0	5	0
Viral infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Viral sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	1 / 13 (7.69%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	1 / 13 (7.69%)	0 / 26 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Vitamin D deficiency			
subjects affected / exposed	2 / 13 (15.38%)	1 / 26 (3.85%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Weight gain poor			
subjects affected / exposed	0 / 13 (0.00%)	1 / 26 (3.85%)	0 / 13 (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
23 July 2018	<p>1. The primary purpose for this protocol amendment was to provide additional clarification about the subject caregiver surveys specific to subjects under the legal age of consent, and to make corrections to the open-label extension period Schedule of Assessments.</p> <p>2. The visit schedule for the 12-lead ECG and renal ultrasound assessments through Year 5 in the open-label extension period was corrected from annually to Month 36 and Month 48 in addition to the EOS visit at Month 60.</p>
19 March 2019	The primary purpose of Amendment 2 was to broaden the subject population by allowing enrollment of subjects with a glomerular filtration rate ≥ 30 mL/min/1.73 m ² and to align clinical objectives and endpoints across the Phase 3 program.
06 May 2020	<p>1. The primary purpose of this protocol amendment was to incorporate Urgent Safety Measures (USMs) to assure the safety of study subjects while minimizing risks to study integrity amid the coronavirus 2019 (COVID-19) pandemic.</p> <p>2. This protocol amendment also incorporated the changes that are not related to USMs. After ongoing review and assessment of the safety data from studies conducted with lumasiran, modifications are designed to enhance subject safety and reduce subject burden regarding blood sampling.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported