Clinical trial results:
ILLUMINATE-B: An Open-Label Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1

Summary

EudraCT number	2018-004014-17
Trial protocol	GB FR DE
Global end of trial date	26 July 2024

Results information

Result version number	v1 (current)
This version publication date	09 February 2025
First version publication date	09 February 2025

Trial information

Trial identification

Sponsor protocol code	ALN-GO1-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03905694
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	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of subcutaneous (SC) lumasiran in infants and young children with confirmed primary hyperoxaluria type 1 (PH1).

Protection of trial subjects:

The legal guardian(s) of each subject signed an informed consent form (ICF) before participating in the study and subjects may have provided assent as per the local and national requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	18
EEA total number of subjects	6

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)	4
Children (2-11 years)	14
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at investigative sites in France, Germany, Israel, the United Kingdom, and the United States from 22 April 2019 to 26 July 2024.

Pre-assignment

Screening details:

A total of 18 subjects with Primary hyperoxaluria type 1 (PH1) were enrolled and treated in this study.

Period 1

Period 1 title	Primary Analysis Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lumasiran

Arm description:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg monthly (QM) for 3 months, followed by maintenance doses of 3.0 mg/kg QM during 6-month primary analysis period (PAP) & QM in 54-month extension period (EP). Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, maintenance doses of 6.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

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

Dosage and administration details:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg QM. Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, then maintenance doses of 6.0 mg/kg Q3M. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg Q3M. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

Number of subjects in period 1	Lumasiran
Started	18
Completed	18

Period 2

Period 2 title	Long-term Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lumasiran

Arm description:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg monthly (QM) for 3 months, followed by maintenance doses of 3.0 mg/kg QM during 6-month primary analysis period (PAP) & QM in 54-month extension period (EP). Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, maintenance doses of 6.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

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Number of subjects in period 2	Lumasiran
Started	18
Completed	18

Baseline characteristics

Reporting groups

Reporting group title	Primary Analysis Period

Reporting group description:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg monthly (QM) for 3 months, followed by maintenance doses of 3.0 mg/kg QM during 6-month primary analysis period (PAP) & QM in 54-month extension period (EP). Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, maintenance doses of 6.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

Reporting group values	Primary Analysis Period	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
In Utero	0	0	
Preterm newborn infants (gestional age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days - 23 months)	4	4	
Children (2 - 11 years)	14	14	
12 - 17 years	0	0	
Adults (18 - 64 years)	0	0	
From 65 - 84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
arithmetic mean	43.7		
standard deviation	± 21.30	-	
Gender categorical Units: Subjects			
Male	8	8	
Female	10	10	
Race Units: Subjects			
White	16	16	
Other	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	16	16	
Spot Urinary Oxalate:Creatinine Ratio Units: mmol/mmol			
arithmetic mean	0.6306		
standard deviation	± 0.42636	-	

End points

End points reporting groups

Reporting group title	Lumasiran

Reporting group description:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg monthly (QM) for 3 months, followed by maintenance doses of 3.0 mg/kg QM during 6-month primary analysis period (PAP) & QM in 54-month extension period (EP). Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, maintenance doses of 6.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

Reporting group title	Lumasiran

Reporting group description:

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Primary: Percentage Change in Spot Urinary Oxalate:Creatinine Ratio From Baseline to Month 6

End point title	Percentage Change in Spot Urinary Oxalate:Creatinine Ratio From Baseline to Month 6 [1]

End point description:

Percent change in spot 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. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) at Month 3 through Month 6.

End point type	Primary

End point timeframe:

Baseline to Month 6

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: Formal statistics were analyzed for this study using the mixed model for repeated measures (MMRM) model. As this is a single-arm study, statistical analysis data could not be presented.

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent change				
least squares mean (standard error)	-71.97 (± 2.706)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in Spot Urinary Oxalate:Creatinine Ratio From Baseline in the Extension Period (Month 6 to End of Study [Month 60])

End point title	Percentage Change in Spot Urinary Oxalate:Creatinine Ratio From Baseline in the Extension Period (Month 6 to End of Study [Month 60])

End point description:

A negative change from Baseline indicates a favorable outcome. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) at Month 6 through Month 60.

End point type	Secondary

End point timeframe:

From Month 6 to Month 60

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent change				
arithmetic mean (standard error)	-74.48 (± 4.246)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Time That Spot Urinary Oxalate:Creatinine Ratio is at or Below the Near-normalization Threshold [≤1.5 × Upper limit of normal (ULN) for Age]

End point title	Percentage of Time That Spot Urinary Oxalate:Creatinine Ratio is at or Below the Near-normalization Threshold [≤1.5 × Upper limit of normal (ULN) for Age]

End point description:

Percentage of time that spot urinary oxalate: creatinine (UOx:Cr) ratio level is at or below ≤1.5xULN is calculated as (cumulative months at or below near normalization threshold divided by cumulative months of assessments*100). Cumulative months in near-normalization was defined as summation across all intervals meeting near-normal threshold & cumulative months of valid assessments was summation across all valid post-baseline collections. ULN levels of spot UOx:Cr ratio where urine oxalate levels were analyzed by enzymatic assay. Age-dependent reference ULN levels of spot UOx:Cr ratio are: 1-1.5 years=0.158; 1.5-2 years=0.138; 2-2.5 years=0.124; 2.5-3 years=0.116; 3-3.5 years=0.102; 3.5-4 years=0.094; 4-4.5 years=0.088; 4.5-5 years=0.082; 5-5.5 years=0.077; 5.5-6 years=0.073.

Efficacy analysis set=all subjects who were treated with Lumasiran & had at least one spot UOx:Cr ratio value at baseline & at least one spot UOx:Cr ratio value from assessment(s) throughout the study duration.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of time				
median (full range (min-max))	68.95 (18.3 to 98.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Spot Urinary Oxalate: Creatinine Ratio From Baseline

End point title	Absolute Change in Spot Urinary Oxalate: Creatinine Ratio From Baseline

End point description:

The absolute change is represented as the ratio of millimoles of urinary oxalate to millimoles of urinary creatinine. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) throughout the study duration.

End point type	Secondary

End point timeframe:

From Baseline to Month 6 and Month 60

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: mmol/mmol				
arithmetic mean (standard error)				
Month 6	-0.4880 (± 0.09127)			
Month 60	-0.5179 (± 0.09929)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Spot Urinary Oxalate: Creatinine Ratio Levels ≤ the ULN for Age

End point title	Percentage of Subjects With Spot Urinary Oxalate: Creatinine Ratio Levels ≤ the ULN for Age

End point description:

The percentage of subjects meeting the criteria (UOx:Cr ratio ≤ the ULN for age) at least at one post-baseline visit were reported for this endpoint. The age-dependent reference ULN levels of spot urinary oxalate to creatinine ratio are as follows: 1-1.5 years=0.158; 1.5-2 years=0.138; 2-2.5 years=0.124; 2.5-3 years=0.116; 3-3.5 years=0.102; 3.5-4 years=0.094; 4-4.5 years=0.088; 4.5-5 years=0.082; 5-5.5 years=0.077; 5.5-6 years=0.073. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) throughout the study duration.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Spot Urinary Oxalate: Creatinine Ratio Levels ≤ 1.5xULN for Age

End point title	Percentage of Subjects With Spot Urinary Oxalate: Creatinine Ratio Levels ≤ 1.5xULN for Age

End point description:

The percentage of subjects meeting the criteria (UOx:Cr ratio ≤ 1.5xULN for age) at least at one post-baseline visit were reported for this outcome measure. The age-dependent reference ULN levels of spot urinary oxalate to creatinine ratio are as follows: 1-1.5 years=0.158; 1.5-2 years=0.138; 2-2.5 years=0.124; 2.5-3 years=0.116; 3-3.5 years=0.102; 3.5-4 years=0.094; 4-4.5 years=0.088; 4.5-5 years=0.082; 5-5.5 years=0.077; 5.5-6 years=0.073.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in Plasma Oxalate From Baseline to End of Study (Month 60)

End point title	Percentage Change in Plasma Oxalate From Baseline to End of Study (Month 60)

End point description:

The Lower Limit of Quantification (LLOQ) was 5.55 micromoles per liter (µmol/L) . A negative change from Baseline indicates a favorable outcome. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) throughout the study duration.

End point type	Secondary

End point timeframe:

From Baseline to Month 6 and Month 60

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent change				
arithmetic mean (standard error)				
Month 6	-32.06 (± 6.711)			
Month 60	-24.78 (± 12.814)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Plasma Oxalate From Baseline to End of Study (Month 60)

End point title	Absolute Change in Plasma Oxalate From Baseline to End of Study (Month 60)

End point description:

The LLOQ was 5.55 µmol/L. A negative change from Baseline indicates a favorable outcome. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) throughout the study duration.

End point type	Secondary

End point timeframe:

From Baseline to Month 6 and Month 60

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: µmol/L				
arithmetic mean (standard error)				
Month 6	-5.03 (± 1.294)			
Month 60	-5.03 (± 1.859)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Lumasiran

End point title	Maximum Observed Plasma Concentration (Cmax) of Lumasiran

End point description:

Cmax was the maximum plasma concentration post-dose within the pharmacokinetic (PK) sampling time frame. Higher Cmax generally indicates higher drug exposure. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=18)	886 (± 58.9)			
Month 6 (n=18)	869 (± 84.0)			
Month 12 (n=17)	1180 (± 83.5)			
Month 18 (n=18)	878 (± 94.0)			
Month 24 (n=17)	790 (± 91.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Plasma Concentration (Tmax) of Lumasiran

End point title	Time to Maximum Observed Plasma Concentration (Tmax) of Lumasiran

End point description:

Tmax was estimated by calculating the time required to reach the maximum plasma concentration (Cmax) after the drug administration. Lower Tmax generally indicates faster drug absorption from the administration site. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hours (h)				
median (full range (min-max))				
Day 1 (n=18)	3.74 (1.87 to 8.1)			
Month 6 (n=18)	4 (1.75 to 10.1)			
Month 12 (n=17)	4 (1.75 to 7.25)			
Month 18 (n=18)	3.64 (1.98 to 10)			
Month 24 (n=17)	3.73 (1.67 to 10.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (t1/2beta) of Lumasiran

End point title	Elimination Half-life (t1/2beta) of Lumasiran

End point description:

Elimination half-life was estimated from the terminal phase of the plasma concentration-time profile post-dose. Shorter half-life generally indicates rapid drug elimination from the body. PK analysis set

included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hours (h)				
median (full range (min-max))				
Day 1 (n=13)	5.46 (1.42 to 10.3)			
Month 6 (n=8)	5.96 (3.04 to 9)			
Month 12 (n=8)	3.52 (1.56 to 6.64)			
Month 18 (n=9)	3.74 (1.62 to 13.9)			
Month 24 (n=8)	4.99 (2.69 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From 0 to 24 Hours (AUC0-24) of Lumasiran

End point title	Area Under the Concentration-time Curve From 0 to 24 Hours (AUC0-24) of Lumasiran

End point description:

AUC0-24 was the total drug exposure calculated as the area under the plasma concentration-time curve from the time of dosing (t = 0) to 24 hours. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours*nanograms per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=14)	8050 (± 37.7)			
Month 6 (n=11)	8450 (± 41.1)			
Month 12 (n=12)	10800 (± 39.3)			
Month 18 (n=12)	8420 (± 57.2)			
Month 24 (n=14)	7420 (± 61.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From 0 to Last Quantifiable Concentration (AUC0-last) of Lumasiran

End point title	Area Under the Concentration-time Curve From 0 to Last Quantifiable Concentration (AUC0-last) of Lumasiran

End point description:

AUC0-last was the total drug exposure calculated as the area under the plasma concentration-time curve from time 0 to the time of the last measurable (quantifiable) concentration (C_last). PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=18)	7870 (± 33.4)			
Month 6 (n=18)	6620 (± 95.5)			
Month 12 (n=17)	8480 (± 76.1)			
Month 18 (n=18)	5770 (± 155.0)			
Month 24 (n=18)	7100 (± 80.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From 0 to infinity (AUC0-infinity) of Lumasiran

End point title	Area Under the Concentration-time Curve From 0 to infinity (AUC0-infinity) of Lumasiran

End point description:

AUC0-infinity was the total drug exposure estimated as the area under the plasma concentration-time curve from time 0 extrapolated to infinity. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=13)	9180 (± 31.7)			
Month 6 (n=8)	8840 (± 40.9)			
Month 12 (n=8)	11900 (± 29.2)			
Month 18 (n=9)	11600 (± 48.6)			
Month 24 (n=8)	9610 (± 48.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F) of Lumasiran

End point title	Apparent Clearance (CL/F) of Lumasiran

End point description:

Apparent clearance was calculated by dividing the area under the plasma concentration-time curve from zero infinity by the dose administered. A higher clearance generally indicates faster elimination from the body. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: liters per hour (L/h)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=13)	8.62 (± 24.0)			
Month 6 (n=8)	10.2 (± 32.3)			
Month 12 (n=9)	7.06 (± 28.3)			
Month 18 (n=9)	6.87 (± 30.6)			
Month 24 (n=8)	8.22 (± 37.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (V/F) of Lumasiran

End point title	Apparent Volume of Distribution (V/F) of Lumasiran

End point description:

Apparent Volume of Distribution generally indicates the extent of drug distribution in the body. PK analysis set included all subjects who had received at least one full dose of Lumasiran and had at least one post-dose blood sample for PK parameters and had evaluable PK data. Overall number analyzed is the number of subjects with data available for analysis. Number analyzed is the number of subjects with data available for analysis at specified timepoints.

End point type	Secondary

End point timeframe:

2 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose on Day 1, Month 6, Month 12, Month 18 and Month 24

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Liters (L)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=13)	57.2 (± 69.8)			
Month 6 (n=8)	81 (± 71.1)			
Month 12 (n=8)	36 (± 75.6)			
Month 18 (n=9)	43.1 (± 107.1)			
Month 24 (n=8)	57.6 (± 70.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point title	Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

End point description:

eGFR [in milliliters per minute per 1.73 meters square (mL/min/1.73m^2)] was calculated from serum creatinine (SCr) based on the Schwartz Bedside Formula for subjects ≥12 months of age at the time of assessment. Efficacy analysis set included all subjects who were treated with Lumasiran and had at least one spot urinary oxalate:creatinine ratio value at baseline and at least one spot urinary oxalate:creatinine ratio value from assessment(s) throughout the study duration. Overall number analyzed is the number of subjects with data available for analysis.

End point type	Secondary

End point timeframe:

From Baseline to Month 6 and Month 60

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mL/min/1.73m^2				
arithmetic mean (standard error)				
Month 6 (n=16) Month 60 (n=16)	-0.263 (± 3.8461) -4.525 (± 4.8873)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs)

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Safety analysis set included all subjects who had received at least one dose of Lumasiran.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Lumasiran			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: subjects	18			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 60 months	
Adverse event reporting additional description:	
Safety analysis set included all subjects who had received at least one dose of Lumasiran.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Lumasiran

Reporting group description:

Subjects weighing <10 kg received loading doses of lumasiran SC injection 6.0 mg/kg monthly (QM) for 3 months, followed by maintenance doses of 3.0 mg/kg QM during 6-month primary analysis period (PAP) & QM in 54-month extension period (EP). Subjects transitioning from <10 kg to ≥10 kg continued QM doses at 3.0 mg/kg until next visit coinciding with a dose for subjects weighing ≥10 kg. Thereafter, subjects followed Q3M dosing until end of study. Subjects weighing ≥10 to <20 kg received 6.0 mg/kg QM for 3 months, maintenance doses of 6.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects ≥20 kg received 3.0 mg/kg QM for 3 months, followed by maintenance doses of 3.0 mg/kg at Months 3 & 6 in PAP & Q3M in EP. Subjects with weight increases to a new dosing category (<10 kg to ≥10 kg/<20 kg to ≥20 kg) followed new regimen for rest of the study/until next dosing category threshold was reached; subjects did not revert to lower-weight dosing schedules if their weight subsequently decreased.

Serious adverse events	Lumasiran		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Ear and labyrinth disorders			
Ear haemorrhage			
alternative dictionary used: MedDRA 25.0 25.0			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection			
alternative dictionary used: MedDRA 25.0 25.0			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lumasiran		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Injection site haematoma			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Injection site reaction			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	4		
Injection site urticaria			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Vessel puncture site haematoma			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	8 / 18 (44.44%)		
occurrences (all)	16		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Laryngeal obstruction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Cough subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 8		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Nasal septum deviation subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 8		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Psychiatric disorders Stress subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Irritability subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Bruxism subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Behaviour disorder subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Blood bilirubin increased			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
SARS-CoV-2 antibody test positive			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Urine analysis abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Hand fracture			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Arthropod sting			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Arthropod bite			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Head injury			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin abrasion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Upper limb fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Ulna fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Congenital, familial and genetic disorders Factor XII deficiency subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Eosinophilia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Leukopenia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Microcytosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 5		

Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Anal pruritus			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Aphthous ulcer			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Dental caries			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	4		
Mouth ulceration			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Teething			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Toothache			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 6 / 18 (33.33%) 13		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Excessive granulation tissue subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 3 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 2 2 / 18 (11.11%) 2		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders			

Arthropathy			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Asymptomatic bacteriuria			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Conjunctivitis bacterial			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Croup infectious			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	4		
Gastroenteritis viral			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastroenteritis			

subjects affected / exposed	5 / 18 (27.78%)			
occurrences (all)	5			
Eye infection				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	4 / 18 (22.22%)			
occurrences (all)	5			
Nasopharyngitis				
subjects affected / exposed	4 / 18 (22.22%)			
occurrences (all)	14			
Pneumonia				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Pneumonia bacterial				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	3 / 18 (16.67%)			
occurrences (all)	4			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Oral herpes				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Otitis media				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	5 / 18 (27.78%)			
occurrences (all)	10			
Tonsillitis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Streptococcal infection				

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Varicella			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Viral pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Iron deficiency			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2019	The following amendments were made to the Protocol: 1. An additional endpoint for the evaluation of the effects of lumasiran on additional measures of urinary oxalate was added. 2. Evaluation of lumasiran on plasma oxalate levels was changed from exploratory to secondary objectives and endpoints. 3. Updated the study sample size from 8 subjects to 20. 4. Updated the analysis population definitions. 5. Description of the efficacy analysis methods was included.
04 May 2020	The following amendments were made to the Protocol: 1. Study visit windows were expanded. 2. Allowed flexibility for scope of physical examination; pregnancy testing when offsite visits occur. 3. Revised and updated informed consent instructions. 4. Revised and updated ethical review instructions. 5. Allowed continuous assessments (collected throughout the study) to be assessed via remote contact.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported