CLINICAL STUDY PROTOCOL

ALN-GO1-004

Protocol Title:	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
Short Title:	A Study to Evaluate Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1 (ILLUMINATE-B)
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2018-004014-17
IND Number:	128941
Protocol Date:	Original protocol, 08 November 2018 Amendment 1.0, 09 August 2019 Amendment 2, 04 May 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA
Sponsor Contact:	

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study.

_____

Alnylam Pharmaceuticals, Inc.

_____

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-004 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title
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

Short Title
A Study to Evaluate Lumasiran in Infants and Young Children with Primary Hyperoxaluria Type 1 (ILLUMINATE-B)

Study Drug
Lumasiran (ALN-GO1)

Phase
Phase 3

Study Center(s)
The study will be conducted at approximately 9 clinical study centers in 5 countries.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the effect of lumasiran on urinary oxalate excretion	• Percent change in urinary oxalate excretion from baseline to Month 6
Secondary	
Extension Phase (Month 6 to End of Study) • Evaluate the long-term effects of lumasiran on urinary oxalate	Extension Phase (Month 6 to End of Study) • Percent change in urinary oxalate excretion from baseline • Percentage of time that spot urinary oxalate:creatinine ratio is at or below the near-normalization threshold (≤1.5 × ULN)
Duration of Study • Evaluate the effects of lumasiran on additional measures of urinary oxalate • Evaluate the effects of lumasiran on plasma oxalate • Characterize the pharmacokinetics (PK) of lumasiran • Evaluate the effect of lumasiran on renal function	Duration of Study • Absolute change in urinary oxalate excretion from baseline • Proportion of patients with urinary oxalate excretion ≤ the upper limit of normal (ULN) and ≤1.5 x ULN • Change (percent and absolute) in plasma oxalate from baseline • Plasma PK parameters of lumasiran • Change from baseline in estimated glomerular filtration rate (eGFR)
Exploratory	
• Evaluate effect of lumasiran on nephrocalcinosis	• Change from baseline in nephrocalcinosis as assessed by renal ultrasound

Objectives	Endpoints
• Evaluate the effect of lumasiran on the occurrence of renal stones • Evaluate the additional pharmacodynamic (PD) parameters of urinary glycolate and plasma glycolate • Evaluate growth parameters • Evaluate developmental milestones • Evaluate experiences of primary hyperoxaluria type 1 (PH1) patients and/or caregivers during treatment with lumasiran • Assess for antidrug antibodies (ADA) against lumasiran	• Change in frequency of renal stone events • Change in urinary glycolate and plasma glycolate • Change in growth parameters (z-scores) from baseline over time • Changes in developmental milestones over time • Changes in patient and/or caregiver experience as evaluated by a patient/caregiver survey • Frequency of ADA
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of adverse events (AEs)

Study Design

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, PK, and PD of lumasiran in infants and young children (<6 years of age) with a documented diagnosis of PH1, as determined by genetic analysis, and relatively preserved renal function.

To be included in the study, patients must reach an estimated gestational age of 37 weeks old (equivalent to full-term infant) but be less than 6 years old. The urinary oxalate:creatinine ratio of at least 2 out of 3 single-void collections during screening must be above the upper limit of normal (ULN) for age. If the patient is ≥12 months old, eGFR must be >45 mL/min/1.73 m^2 based on the Schwartz Bedside Formula. If the patient is <12 months old, then serum creatinine must be at or below the ULN for age.

If the patient is taking therapeutic vitamin B6 (pyridoxine), the patient must have been on a stable regimen for at least 90 days before screening and must remain on this stable regimen until at least the Month 6 visit. Dose adjustments for interval weight gain are acceptable.

Patients will be screened from Day -60 to Day -1 to determine eligibility. Patients who meet all eligibility criteria will be administered open-label lumasiran as a subcutaneous (SC) injection, utilizing weight-based dosing, with dose adjustments for interval weight gain. Patients will receive 3 loading doses (on Day 1, Month 1, and Month 2). Starting at Month 3, patients will receive lumasiran either once monthly (patients weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) at the maintenance dose.

Efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics, and patient and caregiver experience and burden will be assessed. Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, electrocardiograms (ECGs), physical examinations, and concomitant medications.

This study will consist of 2 periods: a 6-month primary analysis period followed by a long-term extension period. During the 6-month primary analysis period, patients will undergo efficacy and safety assessments every 2 weeks for the first month and monthly thereafter. During the long-term extension period of up to 54 months, dosing will continue, and visits will occur at least every-3-months.

Number of Planned Patients
The planned enrollment for this study is 20 patients, including at least 1 patient <12 months of age with weight <10 kg at consent. Patients who discontinue study drug or stop participation in the study prior to Month 6 may be replaced, and the analysis of data collection prior to discontinuation is addressed in the statistical analysis plan.

Diagnosis and Main Eligibility Criteria
This study will include infants and young children (<6 years of age) with a documented diagnosis of PH1 based on urinary oxalate excretion above the upper limit of normal (ULN) for age and confirmed alanine-glyoxylate aminotransferase (*AGXT*) mutations, with relatively preserved renal function at screening (eGFR >45 mL/min/1.73 m^2 based on Schwartz Bedside Formula).

Study Drug, Dose, and Mode of Administration
Lumasiran is an investigational agent comprised of a synthetic, small interfering RNA (siRNA) (drug substance ALN-65585) covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand, designed to target liver *hydroxyacid oxidase 1 (HAO1)* mRNA, decreasing production of glycolate oxidase (GO) and hence reducing hepatic oxalate production.

Lumasiran will be administered as a subcutaneous (SC) injection with weight-based dosing, with dose adjustments for interval weight gain, as follows:

Weight	**Loading Dose (Day 1, Month 1, Month 2)**	**Maintenance Dose (Month 3 and Beyond)**
<10 kg	6.0 mg/kg monthly for 3 months	3.0 mg/kg monthly
≥10 to <20 kg	6.0 mg/kg monthly for 3 months	6.0 mg/kg every 3 months
≥20 kg	3.0 mg/kg monthly for 3 months	3.0 mg/kg every 3 months

For patients who weigh <20 kg, the dose will be based on a weight obtained within 7 days prior to dosing. During periods of time when the COVID-19 pandemic impedes the ability of these patients to travel to the study site or healthcare professionals to go to patients' homes, a weight from up to 6 weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be used to calculate the amount of lumasiran to be administered.

For patients who weigh ≥20 kg, the dose may be based on a weight obtained up to 4 months prior to the planned quarterly dose.

Patients with weight increases crossing the threshold for the next weight-based dosing category (<10 kg to ≥10 kg or <20 kg to ≥20 kg) will follow the new dosing regimen for the remainder of the study or until the next dosing category threshold is reached (ie, patients will not switch back to the lower-weight dosing schedule if their body weight subsequently decreases).

Patients in maintenance dosing who transition from <10 kg to ≥10 kg will continue to receive monthly doses at 3.0 mg/kg until the next visit that coincides with the Schedule of Assessments for patients weighing ≥10 kg. Thereafter, patients will follow every-3-months dosing until the end of the study.

Reference Treatment, Dose, and Mode of Administration
Not applicable.

Duration of Treatment and Study
The duration of treatment with lumasiran is up to 60 months (a month is defined as 28 days). The

estimated total time on study for each patient is up to 62 months, including up to 2 months of screening followed by up to 60 months of treatment.

Statistical Methods

The sample size was determined based on feasibility considerations, not power calculations.

The Safety Analysis Set will include all patients who received at least 1 dose of study drug. The Efficacy Analysis Set will include all patients who received any amount of lumasiran and have at least one valid spot urinary oxalate:creatinine ratio value at baseline and at least one valid spot urinary oxalate:creatinine ratio value from assessment(s) at Month 3 to Month 6. The PK Analysis Set will include all patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters.

The Safety Analysis Set will be used for safety analyses and sensitivity analysis of efficacy. The Efficacy Analysis Set will be used to evaluate efficacy endpoints.

Table 1: Schedule of Assessments –Primary Analysis Period (Screening through Month 6): All Patients

After Month 6, patients with weight <10 kg follow Table 2. Patients with weight ≥10 kg follow Table 4.

Study Period / **Study Visit**		**Screening**	**6-Month Primary Analysis Period**							
			Baseline	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**1**	**15 (±3)**	**29 (±14)**	**57 (±14)**	**85 (±14)**	**113 (±14)**	**141 (±14)**	**169 (±14)**
Informed consent	Section 8.1.1	X								
Demographics	Section 6.1	X								
Medical history	Changes occurring between screening and Day 1 are to be updated prior to dosing. Section 6.1	X	X							
Inclusion/exclusion criteria	Section 4.	X								
Full physical examination	Section 6.5.3	X								X
Abbreviated physical examination	Section 6.5.3		X	X	X	X	X	X	X	
Height/length	Centimeters. Section 6.5.2	X	X		X	X	X	X	X	X
Body weight	Kilograms. Section 5.2.2; Section 6.5.2	X	X		X	X	X	X	X	X
Vital signs	Predose on dosing days. On Day 1 (only), also measured 30 ± 10 minutes postdose. Section 6.5.1	X	X	X	X	X	X	X	X	X
12-lead ECG	Local 12-lead, singlicate, predose ECGs. Section 6.5.4	X	X				X			X
DNA sample for PH1/*AGXT* mutation analysis	Only for patients without documented PH1 genetic analysis.	X								
Exploratory DNA sample (optional)	Where allowed per local regulations. Section 6.6	X								
Clinical laboratory assessments	Serum creatinine and LFTs are repeated if not collected <30 days before Day 1 (Section 5.2.3.1); Section 6.1; Section 6.5.5	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments –Primary Analysis Period (Screening through Month 6): All Patients

After Month 6, patients with weight <10 kg follow Table 2. Patients with weight ≥10 kg follow Table 4.

Study Period / **Study Visit**		**Screening**	**6-Month Primary Analysis Period**							
			Baseline	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**1**	**15 (±3)**	**29 (±14)**	**57 (±14)**	**85 (±14)**	**113 (±14)**	**141 (±14)**	**169 (±14)**
Study drug dosing in patients <10 kg	Dosing must be at least 21 days apart. Section 5.2.2; Table 7		X		X	X	X	X	X	X
Study drug dosing in patients ≥10 kg			X		X	X	X			X
Blood samples for PK analyses	See Table 5 for blood collection timepoints.		X							X
Blood samples for PD analyses	Collected predose, when applicable. Section 6.3.	X	X		X	X	X	X	X	X
24-hour urine collections for PD analyses	At Screening and Month 6, three collections are performed predose. For patients unable to comply, a single catheterized 24- hour collection may be performed. Section 6.2	X								X
Single-void urine collections for PD analysis (3 collections)	Following screening, 3 single-void collections are collected within 7 days predose (first morning voids are preferred). Section 6.2	X			X	X	X	X	X	X
Blood sample for pyridoxine (vitamin B6) levels	Only in patients receiving therapeutic pyridoxine. Do not collect within 6 hours of pyridoxine dose. Section 5.3	X	X				X			X
Renal stone events	Renal stone events are not considered AEs or SAEs. Section 6.3.3	Continuous								
Renal ultrasound	Performed as per procedure manual. Section 6.3.4	X								X
Developmental assessment	Vineland Adaptive Behavior Scale. Section 6.7	X								X
Patient/caregiver experience and impact questionnaire	Section 6.8	X								X
ADA sample	Collect predose. Section 6.5.5.1	X			X		X			X

Table 1: Schedule of Assessments –Primary Analysis Period (Screening through Month 6): All Patients

After Month 6, patients with weight <10 kg follow Table 2. Patients with weight ≥10 kg follow Table 4.

Study Period / **Study Visit**		**Screening**	**6-Month Primary Analysis Period**							
			Baseline	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**1**	**15 (±3)**	**29 (±14)**	**57 (±14)**	**85 (±14)**	**113 (±14)**	**141 (±14)**	**169 (±14)**
Blood and urine samples for exploratory analyses	Single-void urine and blood sample collected predose or prior to visit. Section 6.6	X	X		X		X			X
Review/record AEs	SAEs are collected in the Screening period. Starting on Day 1, all AEs (ie, including SAEs) are collected. Section 6.5.6.2	Continuous								
Prior and concomitant medications	Section 5.3	Continuous								

Abbreviations: ADA=antidrug antibody; AE=adverse event; *AGXT*=alanine-glyoxylate aminotransferase gene; DNA=deoxyribonucleic acid; ECG=electrocardiogram; LFTs=liver function tests; M=Month; PD=pharmacodynamic; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; SAE=serious adverse event; Wk=Week

Note:

- One month is defined as 28 days.
- Assessments are to be performed prior to dosing, where applicable. When scheduled at the same time points and where feasible, the assessments of vital signs and 12-lead ECGs should be performed before physical examinations and blood sample collections.
- Visits and study drug dosing may be conducted offsite where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability), provided the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, renal stone events, adverse events, and healthcare utilization.
- Patients who discontinue from study drug prior to completion of the Month 6 assessments should be encouraged to remain on the study and complete assessments (including 24-hour urine collections but excluding PK assessments) through Month 6. They will also be asked to complete safety follow-up visits once every 3 months, per the safety follow-up schedule (see Table 3 or Table 4), for up to 12 months after the last dose of lumasiran, or until PD recovery (Section 3.3.1) (whichever is earlier). See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 2: Schedule of Assessments – Long-term Extension Period (Month 7 to Month 35): Patient Weight <10 kg

Patients whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with Table 4 and then patients will follow Table 4 until the end of the study. Patients with weight <10 kg follow Table 3 after Month 35.

Study Visit		**M7; M8**	**M9**	**M10; M11**	**M12**	**M13; M14**	**M15**	**M16; M17**	**M18**	**M19; M20**	**M21**	**M22; M23**	**M24**	**M25; M26**	**M27**	**M28; M29**	**M30**	**M31; M32**	**M33**	**M34; M35**
Study Day (±Visit Window)	**Note**	**197, 225 (±14)**	**253 (±14)**	**281, 309 (±14)**	**337 (±14)**	**365, 393 (±14)**	**421 (±14)**	**449, 477 (±14)**	**505 (±14)**	**533, 561 (±14)**	**589 (±14)**	**617, 645 (±14)**	**673 (±14)**	**701, 729 (±14)**	**757 (±14)**	**785, 813 (±14)**	**841 (±14)**	**869, 897 (±14)**	**925 (±14)**	**953, 981 (±14)**
Full physical examination	Section 6.5.3				X				X				X				X			
Abbreviated physical examination	Section 6.5.3	X	X	X		X	X	X			X				X				X	
Height/length	Centimeters. Section 6.5.2		X		X		X		X		X		X		X		X		X	
Body weight	Kilograms. Section 5.2.2; Section 6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	Section 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	Local 12-lead, singlicate, predose ECGs. Section 6.5.4				X								X							
Clinical laboratory assessments	Section 5.2.3.1; Section 6.5.5	X	X	X	X	X	X	X	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only
Study drug dosing	Dosing must be at least 21 days apart. Section 5.2.2; Table 7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for PK analyses	See Table 5 for blood collection timepoints.				X				X				X							
Blood samples for PD analyses	Section 6.3	X (Opt)	X	X (Opt)	X	X (Opt)	X	X (Opt)	X		X		X		X		X		X	
24-hour urine collection for PD analyses (1 collection)	Section 6.2				X				X				X				X			
Single-void urine collections (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2	X (Opt)	X	X (Opt)	X	X (Opt)	X	X (Opt)	X		X		X		X		X		X	

Table 2: Schedule of Assessments – Long-term Extension Period (Month 7 to Month 35): Patient Weight <10 kg

Patients whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with Table 4 and then patients will follow Table 4 until the end of the study. Patients with weight <10 kg follow Table 3 after Month 35.

Study Visit		**M7; M8**	**M9**	**M10; M11**	**M12**	**M13; M14**	**M15**	**M16; M17**	**M18**	**M19; M20**	**M21**	**M22; M23**	**M24**	**M25; M26**	**M27**	**M28; M29**	**M30**	**M31; M32**	**M33**	**M34; M35**
Study Day (±Visit Window)	**Note**	**197, 225 (±14)**	**253 (±14)**	**281, 309 (±14)**	**337 (±14)**	**365, 393 (±14)**	**421 (±14)**	**449, 477 (±14)**	**505 (±14)**	**533, 561 (±14)**	**589 (±14)**	**617, 645 (±14)**	**673 (±14)**	**701, 729 (±14)**	**757 (±14)**	**785, 813 (±14)**	**841 (±14)**	**869, 897 (±14)**	**925 (±14)**	**953, 981 (±14)**
Blood sample for pyridoxine (vitamin B6) levels	Only in patients receiving pyridoxine. Sample is collected >6 hrs. after pyridoxine dose. Section 5.3		X		X															
Renal stone events	Renal stone events are not AEs or SAEs. Section 6.3.3	Continuous																		
Renal ultrasound	Performed as per procedure manual. Section 6.3.4				X								X							
Developmental assessment	Vineland Adaptive Behavior Scale. Section 6.7				X				X				X				X			
Patient/caregiver experience and impact questionnaire	Section 6.8				X				X				X				X			
ADA sample	Collect predose. Section 6.5.5.1		X		X				X				X				X			
Blood and urine samples for exploratory analyses	Single-void urine and blood sample collected predose or prior to visit. Section 6.6		X				X				X				X				X	
Review/ record AEs	Section 6.5.6.2	Continuous																		
Prior and concomitant medications	Section 5.3	Continuous																		

Abbreviations: ADA=antidrug antibody; AE=adverse event; ECG=electrocardiogram; ET=early termination; hrs=hours; M=month; Opt=optional; PD=pharmacodynamic; PK=pharmacokinetic; Pts=patients; SAE=serious adverse event

Notes:

- One month is defined as 28 days.

- Assessments are to be performed prior to dosing, where applicable. When scheduled at the same time points and where feasible, the assessments of vital signs and 12-lead ECGs should be performed before physical examinations and blood sample collections.
- Visits and study drug dosing may be conducted offsite where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability), provided the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, renal stone events, adverse events, and healthcare utilization.
- Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete ET assessments and to complete safety follow-up visits once every 3 months, per the safety follow-up schedule (see Table 3 or Table 4), for up to 12 months after the last dose of lumasiran, or until PD recovery (Section 3.3.1) (whichever is earlier). See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 3: Schedule of Assessments – Long-term Extension Period (Month 36 to End of Study): Patient Weight <10 kg

Patients whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with Table 4. Patients will then follow Table 4 until the end of the study.

Study Period		**Long-term Extension Period**														**EOT**	**EOS/ ET**	**Safety Follow-up** (Pts who DC treatment)
Study Visit		**M36**	**M37; M38**	**M39**	**M40; M41**	**M42**	**M43; M44**	**M45**	**M46; M47**	**M48**	**M49; M50**	**M51**	**M52; M53**	**M54**	**M55; M56**	**M57**	**M60**	
Study Day (±Visit Window)	**Notes**	**1009 (±14)**	**1037, 1065 (±14)**	**1093 (±14)**	**1121, 1149 (±14)**	**1177 (±14)**	**1205, 1233 (±14)**	**1261 (±14)**	**1289, 1317 (±14)**	**1345 (±14)**	**1373, 1401 (±14)**	**1429 (±14)**	**1457, 1485 (±14)**	**1513 (±14)**	**1541, 1569 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Full physical examination	Section 6.5.3	X				X				X				X			X	
Abbreviated physical examination	Section 6.5.3			X				X				X				X		X
Height/length	Centimeters. Section 6.5.2	X		X		X		X		X		X		X		X	X	X
Body weight	Kilograms. Section 5.2.2; Section 6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	Section 6.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	Local 12-lead, singlicate, predose ECGs. Section 6.5.4	X								X							X	
Clinical laboratory assessments	Section 5.2.3.1; Section 6.5.5	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	X	X
Study drug dosing	Dosing must be at least 21 days apart. Section 5.2.2; Table 7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for PD analyses	Section 6.3	X		X		X		X		X		X		X		X	X	X

Table 3: Schedule of Assessments – Long-term Extension Period (Month 36 to End of Study): Patient Weight <10 kg

Patients whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with Table 4. Patients will then follow Table 4 until the end of the study.

Study Period		**Long-term Extension Period**														**EOT**	**EOS/ ET**	**Safety Follow-up**
Study Visit		**M36**	**M37; M38**	**M39**	**M40; M41**	**M42**	**M43; M44**	**M45**	**M46; M47**	**M48**	**M49; M50**	**M51**	**M52; M53**	**M54**	**M55; M56**	**M57**	**M60**	(Pts who DC treatment)
Study Day (±Visit Window)	**Notes**	**1009 (±14)**	**1037, 1065 (±14)**	**1093 (±14)**	**1121, 1149 (±14)**	**1177 (±14)**	**1205, 1233 (±14)**	**1261 (±14)**	**1289, 1317 (±14)**	**1345 (±14)**	**1373, 1401 (±14)**	**1429 (±14)**	**1457, 1485 (±14)**	**1513 (±14)**	**1541, 1569 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
24-hour urine collection for PD analyses (1 collection)	Section 6.2	X				X				X				X			X	
Single-void urine collections (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2	X								X							X	X
Single-void urine collections (1 collection)				X		X		X				X		X		X		
Renal stone events	Renal stone events are not AEs or SAEs. Section 6.3.3	Continuous																
Renal ultrasound	Performed as per procedure manual. Section 6.3.4	X								X							X	
Developmental assessment	Vineland Adaptive Behavior Scale. Section 6.7	X				X				X				X			X	
Patient/caregiver experience and impact questionnaire	Section 6.8	X				X				X				X			X	
ADA sample	Collect predose. Section 6.5.5.1	X				X				X				X			X	X
Blood and urine samples for exploratory analyses	Single-void urine and blood sample collected predose or prior to visit. Section 6.6			X				X				X				X	X	
Review/ record AEs	Section 6.5.6.2	Continuous																

Table 3: Schedule of Assessments – Long-term Extension Period (Month 36 to End of Study): Patient Weight <10 kg

Patients whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with Table 4. Patients will then follow Table 4 until the end of the study.

Study Period		**Long-term Extension Period**													**EOT**	**EOS/ ET**	**Safety Follow-up** (Pts who DC treatment)
Study Visit		**M36**	**M37; M38**	**M39**	**M40; M41**	**M42**	**M43; M44**	**M45**	**M46; M47**	**M48**	**M49; M50**	**M51**	**M52; M53**	**M54**	**M55; M56**	**M57**	**M60**	
Study Day (±Visit Window)	**Notes**	**1009 (±14)**	**1037, 1065 (±14)**	**1093 (±14)**	**1121, 1149 (±14)**	**1177 (±14)**	**1205, 1233 (±14)**	**1261 (±14)**	**1289, 1317 (±14)**	**1345 (±14)**	**1373, 1401 (±14)**	**1429 (±14)**	**1457, 1485 (±14)**	**1513 (±14)**	**1541, 1569 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Prior and concomitant medications	Section 5.3	Continuous																

Abbreviations: ADA=antidrug antibody; AE=adverse event; DC=discontinue; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; hrs=hours; M=month; PD=pharmacodynamic; PK=pharmacokinetic; Pts=patients; SAE=serious adverse event

Notes:

- One month is defined as 28 days.
- Assessments are to be performed prior to dosing, where applicable. When scheduled at the same time points and where feasible, the assessments of vital signs and 12-lead ECGs should be performed before physical examinations and blood sample collections.
- Visits and study drug dosing may be conducted offsite where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability), provided the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, renal stone events, adverse events, and healthcare utilization.
- Patients who discontinue study drug early will be asked to return for their next scheduled visit to complete ET assessments and to complete safety follow-up visits once every 3 months, per the safety follow-up schedule in this table, for up to 12 months after the last dose of lumasiran, or until PD recovery (Section 3.3.1) (whichever is earlier). See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 4: Schedule of Assessments – Long-term Extension Period (Month 9 to End of Study): Patient Weight ≥10 kg

Patients following Table 2 or Table 3 whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with this table. Patients will then follow this table until the end of the study.

Study Period		**Long-term Extension Period**																**EOT**	**EOS/ ET**	**Safety Follow-up** (Pts who DC treatment)
Study Visit		**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**	**M39**	**M42**	**M45**	**M48**	**M51**	**M54**	**M57**	**M60**	
Study Day (±Visit Window)	**Notes**	**253 (±28)**	**337 (±28)**	**421 (±28)**	**505 (±28)**	**589 (±28)**	**673 (±28)**	**757 (±28)**	**841 (±28)**	**925 (±28)**	**1009 (±28)**	**1093 (±28)**	**1177 (±28)**	**1261 (±28)**	**1345 (±28)**	**1429 (±28)**	**1513 (±28)**	**1597 (±28)**	**1681 (±28)**	**Every 84 days (±28)**
Full physical examination	Section 6.5.3		X		X		X		X		X		X		X		X		X	
Abbreviated physical examination	Section 6.5.3	X		X		X														X
Height/length	Centimeters. Section 6.5.2	X	X		X		X		X		X		X		X		X		X	X
Body weight	Kilograms. Section 6.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	Section 6.5.1	X	X	X	X	X	X		X		X		X		X		X		X	X
12-lead ECG	Local 12-lead, singlicate, predose ECGs. Section 6.5.4		X				X				X				X				X	
Clinical laboratory assessments	Section 5.2.3.1; Section 6.5.5	X	X	X	X	X	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	X
Pregnancy testing	Females of child-bearing potential only. Section 6.5.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dosing	Dosing must be at least 21 days apart. Section 5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for PK analyses	See Table 5 for timepoints.		X		X		X													
Blood samples for PD analyses	Section 6.3	X	X	X	X	X	X	X (opt)	X	X (opt)	X	X (opt)	X	X (opt)	X	X (opt)	X	X (opt)	X	X

Table 4: Schedule of Assessments – Long-term Extension Period (Month 9 to End of Study): Patient Weight ≥10 kg

Patients following Table 2 or Table 3 whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with this table. Patients will then follow this table until the end of the study.

Study Period		**Long-term Extension Period**																**EOT**	**EOS/ ET**	**Safety Follow-up** (Pts who DC treatment)
Study Visit		**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**	**M39**	**M42**	**M45**	**M48**	**M51**	**M54**	**M57**	**M60**	
Study Day (±Visit Window)	**Notes**	**253 (±28)**	**337 (±28)**	**421 (±28)**	**505 (±28)**	**589 (±28)**	**673 (±28)**	**757 (±28)**	**841 (±28)**	**925 (±28)**	**1009 (±28)**	**1093 (±28)**	**1177 (±28)**	**1261 (±28)**	**1345 (±28)**	**1429 (±28)**	**1513 (±28)**	**1597 (±28)**	**1681 (±28)**	**Every 84 days (±28)**
24-hour urine collection for PD analyses (1 collection)	Section 6.2		X		X		X		X		X		X		X		X		X	
Single-void urine collections (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2	X	X	X	X	X	X		X		X				X				X	X
Single-void urine collection (1 collection)								X		X		X	X	X		X	X	X		
Renal stone events	Renal stone events are not AEs or SAEs. Section 6.3.3	Continuous																		
Renal ultrasound	Performed as per procedure manual. Section 6.3.4		X				X				X				X				X	
Developmental assessment	Vineland Adaptive Behavior Scale. Section 6.7		X		X		X		X		X		X		X		X		X	
Patient/ caregiver experience and impact questionnaire	Section 6.8		X		X		X		X		X		X		X		X		X	
ADA sample	Collect predose. Section 6.5.5.1	X	X		X		X		X		X		X		X		X		X	X

Table 4: Schedule of Assessments – Long-term Extension Period (Month 9 to End of Study): Patient Weight ≥10 kg

Patients following Table 2 or Table 3 whose weight increases to ≥10 kg continue monthly dosing until the next visit that coincides with this table. Patients will then follow this table until the end of the study.

Study Period		**Long-term Extension Period**																**EOT**	**EOS/ ET**	**Safety Follow-up** (Pts who DC treatment)
Study Visit		**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**	**M33**	**M36**	**M39**	**M42**	**M45**	**M48**	**M51**	**M54**	**M57**	**M60**	
Study Day (±Visit Window)	**Notes**	**253 (±28)**	**337 (±28)**	**421 (±28)**	**505 (±28)**	**589 (±28)**	**673 (±28)**	**757 (±28)**	**841 (±28)**	**925 (±28)**	**1009 (±28)**	**1093 (±28)**	**1177 (±28)**	**1261 (±28)**	**1345 (±28)**	**1429 (±28)**	**1513 (±28)**	**1597 (±28)**	**1681 (±28)**	**Every 84 days (±28)**
Blood and urine samples for exploratory analyses	Single-void urine and blood sample collected predose or prior to visit. Section 6.6	X		X		X	X		X		X		X		X		X		X	
Review/ record AEs	Section 6.5.6.2	Continuous																		
Prior and concomitant medications	Section 5.3	Continuous																		

Abbreviations: ADA=antidrug antibody; AE=adverse event; DC=discontinue; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; hrs=hours; M=month; PD=pharmacodynamic; PK=pharmacokinetic; Pts=patients; SAE=serious adverse event

Notes:

- One month is defined as 28 days.
- Assessments are to be performed prior to dosing, where applicable. When scheduled at the same time points and where feasible, the assessments of vital signs and 12-lead ECGs should be performed before physical examinations and blood sample collections.
- Visits and study drug dosing may be conducted offsite where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability), provided the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, renal stone events, adverse events, and healthcare utilization.
- Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete ET assessments and to complete safety follow-up visits once every 3 months, per the safety follow-up schedule, for up to 12 months after the last dose of lumasiran, or until PD recovery (Section 3.3.1) (whichever is earlier). See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 5: Pharmacokinetic Time Points: All Patients

Study Visit	Protocol Time (hh:mm)
Day 1, Month 6, Month 12, Month 18, and Month 24 study visits.	02:00 (±20 minutes)
	04:00 (±30 minutes)
	08:00 (±1 hour)
	12:00 (±2 hour)
	24:00 (±3 hours)

Abbreviations: hh:mm=hour:minute; PK=pharmacokinetic; SAE=serious adverse event
Note:

- Blood samples for PK assessment may be collected at 8, 12, and 24 hours postdose as feasible during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes.
- The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded.
- If an SAE occurs associated with dosing, an additional PK sample may be collected at 4 to 8 hours postdose on the day of dosing, where blood volume permits (see Section 6.5.5.4).
- See Section 7.2.7 for additional information on PK assessments.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AGT	Alanine-glyoxylate aminotransferase
AGXT	Alanine-glyoxylate aminotransferase gene
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
BSA	Body surface area
CDC	US Centers for Disease Control and Prevention
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulations
CL/F	Apparent clearance
COVID-19	Coronavirus disease 2019
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ET	Early termination
EQ-5D	Euro Quality of Life Health State Profile Questionnaire
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GO	Glycolate oxidase
24h	24 hours
HAO1	Hydroxyacid oxidase 1
HBV	Hepatitis B virus

Abbreviation	Definition
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reactions
LFT	Liver function tests
MAD	Multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mMol	Millimoles
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamic
PH1	Primary hyperoxaluria type 1
PK	Pharmacokinetic
PT	Preferred Term
q3M	Once every 3 months
qM	Monthly (every 28 days)
RNA	Ribonucleic acid
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCr	Serum creatinine
siRNA	Small interfering RNA
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
$t_{½\beta}$	Elimination half-life
t_{max}	Time to maximum plasma concentration

Abbreviation	Definition
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WHO	World Health Organization

1. INTRODUCTION

1.1. Disease Overview

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disease characterized by excessive oxalate production by the liver and consequent hyperoxaluria. PH1 is caused by mutations in the alanine-glyoxylate aminotransferase (*AGXT*) gene, which encodes the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). As a consequence of AGT deficiency, glyoxylate accumulates and is oxidized to oxalate in the hepatocyte and ultimately transported to the kidneys for excretion. Oxalate, in the form of its calcium salt, is excreted almost entirely by the kidney. Due to its insolubility, calcium oxalate can crystallize readily in the urinary tract. In PH1, excess urinary oxalate results in recurrent nephrolithiasis and/or nephrocalcinosis, which can lead to pain, infections, progressive kidney disease and failure, along with reduced quality of life.[Cochat and Rumsby 2013] As renal function declines, elimination of oxalate is further reduced, such that calcium oxalate accumulates in bone, vasculature, skin, retina, heart, and nervous system, resulting in severe end-organ damage.[Cochat and Rumsby 2013] This devastating condition, systemic oxalosis, arises when the estimated glomerular filtration rate (eGFR) has declined to below 30 to 45 mL/min/1.73 m^2.[Cochat and Rumsby 2013] Without treatment, the disease progresses inexorably, and death from end-stage renal disease (ESRD) and/or complications of oxalosis is inevitable.[Cochat and Rumsby 2013; Harambat 2010; van der Hoeven 2012]

Over 150 mutations in *AGXT* have been described.[Williams 2009] While there are broad genotype–phenotype associations with the underlying causative defect, patients can present with very different symptoms, disease course, including timing of an individual's eGFR decline, and treatment response.[Danpure 2014; Hoppe 1997] Patients progress at various rates and an event that leads to acute or chronic worsening, such as an obstructive kidney stone or episode of dehydration, can occur at any time.

The incidence of PH1 is approximately 1 in 120,000 live births, and the prevalence is 1 to 3 per million in North America and Europe.[Cochat and Rumsby 2013; Hopp 2015; Hoppe 2010] The disease is more prevalent in areas where consanguineous marriages are common, especially in the Middle East and Northern Africa.[Al-Eisa 2004; Boualla 2015; Frishberg 2005; Kamoun and Lakhoua 1996]

PH1 often presents as a pediatric disease, but many patients remain undiagnosed for years after the initial clinical manifestations of the disease.[Lieske 2005; Mandrile 2014; van Woerden 2003] A recently published analysis of 247 patients with PH1 from 206 pedigrees in the Rare Kidney Stone Consortium PH Registry demonstrated a median age of first symptoms at 5.2 years of age and a cumulative renal survival of 76%, 43%, and 12% at 20 years, 40 years, and 60 years, respectively.[Hopp 2015] Similarly, an analysis of 526 patients with PH1 published by the OxalEurope Consortium indicated a median age of disease symptom onset of 3.9 years and a median age of diagnosis of 8.1 years.[Mandrile 2014] Overall, 43% of all patients diagnosed with PH1 had already progressed to ESRD at the time of diagnosis. The deterioration of renal function highlights the importance of investigating potentially disease-modifying interventions as soon as possible after diagnosis.

There are no approved therapies for the treatment of PH1 and the current standard of care is burdensome to patients and their families. Disease management is based on supportive measures, including high fluid intake and crystallization inhibitors to increase urinary oxalate solubility, and treatment of disease complications such as urinary tract stones and infections. A minority of patients experience oxalate lowering with therapeutic doses of pyridoxine (vitamin B6). Dietary modification plays a minor role in treatment since endogenous oxalate production far exceeds dietary intake. Patients progressing to, or presenting with ESRD, require intense kidney dialysis. Dialysis is not viewed as an effective therapy for PH1, but rather serves as a bridge to a liver-kidney transplant or as an alternative to no therapy at all. Dialysis is often inadequate to effectively offload accumulating oxalate, and systemic oxalosis with end organ damage may develop despite this burdensome treatment. Dialysis regimens for PH1 are more frequent than conventional dialysis, predisposing to increased risk of complications. Combined liver-kidney transplantation offers potentially curative therapy, but is limited due to restricted availability, complications associated with the procedure, ethical considerations in resource-poor settings[Cochat and Rumsby 2013], and intense use of health care resources.

PH1 can progress to be a serious, severely debilitating disease with significant morbidity and mortality and negatively impacts quality of life. Limited and burdensome management options for PH1 outlined above highlight the serious unmet need for a safe and efficacious treatment for patients with this devastating disease.

1.2. Lumasiran

Alnylam Pharmaceuticals, Inc. (the Sponsor) is developing lumasiran (ALN-GO1), an investigational agent comprised of a synthetic, small interfering RNA (siRNA) (drug substance ALN-65585) covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand, designed to target liver *hydroxyacid oxidase 1 (HAO1)* mRNA, blocking production of glycolate oxidase (GO) and hence reducing hepatic oxalate production, which is the underlying cause of the morbidity and mortality associated with PH1.

Lumasiran is currently in development for treatment of PH1 in adult and pediatric patients.

A detailed description of the chemistry, pharmacology, efficacy, and safety of lumasiran is provided in the current edition of the Investigator's Brochure.

1.2.1. Summary of Nonclinical Data with Lumasiran

The pharmacology, safety pharmacology, drug metabolism and pharmacokinetics (PK), and toxicology of lumasiran were evaluated in a series of in vitro and in vivo nonclinical studies.

Lumasiran was pharmacologically active in all tested species. Subcutaneous (SC) administration of lumasiran demonstrated potent, dose-dependent pharmacologic activity resulting in reduced hepatic *HAO1* mRNA levels with the expected increases in glycolate levels in wild-type and diseased animals and subsequent reductions in urinary oxalate in diseased animals.

Genetic toxicity studies (bacterial reverse mutation, human peripheral blood lymphocyte chromosomal aberrations, and rat bone marrow micronucleus) assays were all negative at International Conference on Harmonisation (ICH) S2 (R1) limit doses.

The nonclinical toxicology program for lumasiran includes a repeat-dose exploratory toxicology study in rats, and a series of Good Laboratory Practice (GLP) studies, which include developmental and reproductive studies in rats and rabbits, a pilot study in juvenile rats, and repeat-dose studies of up to 25- and 36-weeks in duration in rats and nonhuman primates, respectively. To support inclusion of pediatric patients, the GLP repeat-dose rat studies were initiated with post-weaning animals that were 4 to 5 weeks old. Additionally, a GLP-compliant pilot neonatal and juvenile rat toxicology study in the rat that was initiated in postnatal-day 4 pups, and continued through postnatal-day 33, did not identify any evidence of potential developmental safety concerns due to either the toxicology or pharmacology of lumasiran.

The results of these nonclinical toxicology studies demonstrate a favorable safety profile for lumasiran and supports the use of lumasiran in the planned pivotal clinical studies in pediatric (as young as full-term neonates) and adult patients with PH1.

A summary of nonclinical studies is included in the current edition of the Investigator's Brochure.

1.2.2. Summary of Clinical Data with Lumasiran

Lumasiran is being investigated in 3 clinical studies. Study ALN-GO1-001 is a Phase 1/2 study, conducted in 2 parts (single-ascending dose [SAD; Part A] and multiple-ascending dose [MAD; Part B]), in healthy adult subjects and adult and pediatric patients (≥ 6 years old) with PH1. The primary objective of Study ALN-GO1-001 is to evaluate the safety and tolerability of subcutaneously-administered lumasiran. Secondary and exploratory objectives include the characterization of plasma and urine PK and the evaluation of the pharmacodynamic (PD) effect, including glycolate and oxalate levels (Part B only). In this study, healthy adult subjects in Part A were randomized to receive a single-blind dose of lumasiran (0.3-6.0 mg/kg) or placebo (6:2). In Part B, patients ≥6 years of age with PH1 and preserved renal function (eGFR >45 mL/min/1.73 m^2) were randomized 3:1 to receive single-blind doses of lumasiran or placebo at 1.0 mg/kg monthly for 3 doses, 3.0 mg/kg monthly for 3 doses, or 3.0 mg/kg every-3-months for 2 doses. Patients in Part B on placebo transitioned to the open-label portion of the study to receive lumasiran.

Study ALN-GO1-002 is a Phase 2 open-label extension study to evaluate the long-term safety, PK, and PD of lumasiran in patients with PH1 who complete Study ALN-GO1-001.

Study ALN-GO1-003 (ILLUMINATE-A) is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lumasiran in children and adults (≥6 years old) with a documented diagnosis of PH1, elevated urinary oxalate, and relatively preserved renal function (GFR >45 mL/min/1.73m^2). The study consists of a randomized, controlled, double-blinded primary analysis period of 6 months, followed by an extension phase for 54 months during which all patients are treated with lumasiran.

Available safety data from clinical studies indicate that lumasiran has an acceptable safety and tolerability profile across all dosing regimens with no drug-related serious adverse events (SAEs) or study discontinuations attributed to drug administration. Urinary oxalate levels are an important measurement in patients with PH1. Preliminary data from ALN-GO1-001 showed a mean maximal reduction in urinary oxalate of >60% in patients with PH1 in Part B of the study

and a durable suppression of urinary oxalate over time. Reduction in urinary oxalate was evident at the first assessment time point at Day 29.

Further information on the chemistry, pharmacology, efficacy, and safety of lumasiran is provided in the current edition of the Investigator's Brochure.

1.3. Study Design Rationale

Lumasiran is proposed to reduce urinary oxalate production resulting in lower urinary oxalate excretion in patients with PH1. In preclinical models and patients with PH1, SC administration of lumasiran demonstrated potent, dose-dependent pharmacologic activity resulting in substantial reductions in urinary oxalate.[Liebow 2017]

Urinary oxalate excretion is the most sensitive and clinically relevant marker that directly relates to the PH1 disease pathophysiology in this population and is used clinically for diagnosis and management of patients with PH1 who have preserved renal function. Elevated urinary oxalate is the direct cause of kidney stones and renal failure in patients with PH1. Lowered urinary oxalate excretion is expected to provide clinical benefit in patients with preserved renal function by directly targeting the cause of the disease: toxic urinary oxalate levels that lead to oxalate crystallization in the kidneys and urinary tract. Reduced urinary oxalate excretion therefore is expected to reduce kidney stone burden and potentially stabilize renal function.

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, PK, and PD of lumasiran in pediatric patients younger than 6 years old at consent with PH1 and relatively preserved renal function. The primary endpoint for the study is percent change in urinary oxalate excretion from baseline to Month 6. To evaluate the long-term safety and efficacy of lumasiran, all patients will continue to receive open-label lumasiran for up to 54 months. Patients will continue their current standard of care regimen, which may include hyperhydration, crystallization inhibitors, and/or pyridoxine therapy, until the Month 6 visit, after which they can adjust per the recommendations of their treating physician. Current disease management options are presented in Section 1.1.

Lumasiran is currently being investigated in 3 clinical studies in children and adults (≥6 years of age) with PH1 and relatively preserved renal function. In this study, lumasiran will be evaluated in a similar but younger patient population (infants and young children <6 years of age). Enrolling infants and young pediatric patients in this study is acceptable given that lumasiran has been well tolerated in children ≥6 years of age, that PH1 presents as a pediatric disease with life-threatening consequences, and there is a high unmet medical need in this population.

1.4. Dose Rationale

Preclinical data and clinical data from study ALN-GO1-001 Parts A and B in healthy subjects and in PH1 patients 6 years old and above were used to support PKPD modeling and dose selection for this study. Population PKPD modeling in patients with PH1 demonstrated dose-dependent oxalate reductions over the dose range studied (1.0 to 6.0 mg/kg once monthly or once every 3 months SC administration). The PKPD model indicated that monthly administration leads to a more rapid decline in urinary oxalate levels compared to every-3-months dosing. A combination of monthly dosing in a loading phase and then dosing every 3 months in a maintenance phase achieves the goals of rapid and consistent lowering of urinary oxalate to

normal or near normal levels in PH1 patients. Thus, based on PKPD modeling and simulation, the proposed lumasiran dose for pediatric and adult PH1 patients ages 6 and above is as follows: 3.0 mg/kg monthly x 3 doses (loading dose) followed by 3.0 mg/kg every-3-months (maintenance dose) starting 1 month after the last loading dose. At steady state, this regimen is expected to achieve approximately 90% target suppression and reduce urinary oxalate to 0.44 mMol/24h/body surface area (BSA) (see Table 6).

For the current study (Study ALN-GO1-004), the goal of dose selection is to achieve similar reductions in hepatic oxalate production and similar lumasiran systemic exposure relative to PH1 patients 6 years old and above.

The modeling and simulation approach in infants and children younger than 6 years old considered the changing rate of body weight and relative liver size in this young population. The body weight of children nearly triples during the first year of life increasing from a median weight of 3.5 kg at birth to about 10 kg at 1 year of age (Centers for Disease Control and Prevention [CDC] Growth Chart [Kuczmarski 2002]). Subsequently, the annual rate of body weight gain decreases to about 20% per year up to 6 years of age. Furthermore, published reports and data from the United States National Centers for Health Statistics indicate children have proportionally larger liver size relative to body weight compared to adults. [Johnson 2005; National Centers for Health Statistics 2018] For an individual in the 0 to 1 year, 1 to 6 years, and 6 years old age categories, the mean liver weight as a percentage of body weight were 3.5%, 2.9%, and 2.0%, respectively, indicating that younger children are expected to have lower hepatocyte drug concentrations at a given dose level. Moreover, based on allometric principles, children have faster drug clearance and drug clearance decreases with increasing weight. Thus, considering the rapid growth rate, higher relative liver size, and faster drug clearance, children require a higher mg/kg dose to achieve similar systemic concentration and target suppression. It should be noted that mg/kg dosing leads to a smaller absolute dose in children due to their lower body weight.

Body weight categories for dose selection in this study were determined using CDC growth chart data. For infants from birth to 1 year of age, the corresponding median weight ranges are 3.5 to 10 kg, respectively. For children ages 1 to 6 years old, the corresponding median weight ranges are 10 to 20 kg. For children 6 years old and above, the median weight is 20 kg and above.

Based on PKPD modeling and simulation, for children weighing less than 10 kg, corresponding to children from birth up to 1 year old, the proposed regimen is 6.0 mg/kg monthly x 3 doses (loading) followed by 3.0 mg/kg monthly (maintenance). For children weighing ≥10 to 20 kg, which represent children ages 1 to 6 years old, the proposed regimen is 6.0 mg/kg monthly x 3 doses (loading) followed by 6.0 mg/kg every-3-months (maintenance). The proposed regimens in children birth to 6 years old are expected to result in target suppression of approximately 87 to 90% and median urinary oxalate levels 0.41 to 0.47 mMol/24h/BSA (see Table 6).

Table 6: Proposed Lumasiran Dosing Regimen in Pediatric and Adult PH1 Patients and Predicted Target Suppression and Urinary Oxalate Levels at Steady State

Body Weight (kg)	Regimen		Predicted GO Suppression[a] (%)	Predicted[a,b] Median Urinary Oxalate (mMol/24h/BSA)
	Loading	Maintenance		
<10	6.0 mg/kg qM x3	3.0 mg/kg qM	86.5%	0.47
10 – <20	6.0 mg/kg qM x3	6.0 mg/kg q3M	90.2%	0.41
≥20	3.0 mg/kg qM x3	3.0 mg/kg q3M	89.7%	0.44

Abbreviations: BSA=body surface area; GO=glycolate oxidase; h=hour; qM=monthly (every 28 days), q3M=once every 3 months; UOx=urinary oxalate
[a] All values are at steady state.
[b] Values are for baseline UOx of 2.0 mMol/24h/BSA

1.5. Benefit-Risk Assessment

PH1 is a rare autosomal recessive disease characterized by excessive oxalate production by the liver leading to excessive urinary oxalate and varying types and degrees of renal disease, progressing to end-stage renal disease. Systemic accumulation of calcium oxalate results in severe end-organ damage. Without treatment, the disease progresses, and patients die from end-stage renal disease and/or complication of oxalosis.

Lumasiran is designed to reduce hepatic production of oxalate. Based on the available data from nonclinical studies and the Phase 1/2 clinical study ALN-GO1-001, lumasiran, administered subcutaneously, demonstrated a potent, dose-dependent inhibition of glycolate oxidase resulting in decreased urinary oxalate and increased plasma and urinary glycolate. Unlike oxalate, glycolate is highly soluble and readily excreted in the urine. Thus, by reducing the production of oxalate, lumasiran is expected to ameliorate the signs and symptoms of PH1 and alter the clinical course in patients across the spectrum of disease, irrespective of age and disease stage.

Based on the available safety data from the Phase 1/2 clinical study, lumasiran has been well tolerated with a favorable safety profile. Most adverse events (AEs) have been mild or moderate in severity. There have been no severe or serious adverse events related to study drug. Transient, mild injection site reactions (ISRs) have been observed but have not resulted in any treatment discontinuations or dose adjustments. No clinically significant laboratory or hematologic changes have been observed.

Given the biological target of lumasiran, the available nonclinical and clinical data, and mode of administration, important potential risks for lumasiran are injection site reactions and liver function test abnormalities. During the study, patients will be closely monitored, including evaluation of injection sites, laboratory monitoring for liver function test abnormalities, along with other standard hematology and blood chemistries. The study has specific inclusion and exclusion criteria to ensure that patients have adequate hepatic function and specific rules for dose withholding and stopping have been incorporated in the protocol for abnormalities in liver function tests. As the risk of embryofetal toxicity is currently unknown, females who achieve

child-bearing potential during the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use contraception as specified in the protocol (see Section 5.5.1).

An external, independent Data Monitoring Committee (DMC) will monitor and ensure the safety of trial participants (see Section 3.7).

Based on the emerging efficacy and available safety data from the Phase 1/2 clinical study (ALN-GO1-001) and nonclinical studies, the benefit-risk assessment supports the evaluation of lumasiran in a Phase 3 study in infants and young children with PH1.

Detailed information about the known and expected benefits and risks of lumasiran may be found in the current edition of the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Evaluate the effect of lumasiran on urinary oxalate excretion	• Percent change in urinary oxalate excretion from baseline to Month 6
Secondary	
Extension Phase (Month 6 to End of Study) • Evaluate the long-term effects of lumasiran on urinary oxalate	Extension Phase (Month 6 to End of Study) • Percent change in urinary oxalate excretion from baseline • Percentage of time that spot urinary oxalate:creatinine ratio is at or below the near-normalization threshold (≤1.5 × ULN)
Duration of Study • Evaluate the effects of lumasiran on additional measures of urinary oxalate • Evaluate the effects of lumasiran on plasma oxalate • Characterize the pharmacokinetics (PK) of lumasiran • Evaluate the effect of lumasiran on renal function	Duration of Study • Absolute change in urinary oxalate excretion from baseline • Proportion of patients with urinary oxalate excretion ≤ the upper limit of normal (ULN) and ≤ 1.5 x ULN • Change (percent and absolute) in plasma oxalate from baseline • Plasma PK parameters of lumasiran • Change from baseline in estimated glomerular filtration rate (eGFR)
Exploratory	

Objectives	Endpoints
• Evaluate effect of lumasiran on nephrocalcinosis • Evaluate the effect of lumasiran on the occurrence of renal stones • Evaluate the additional pharmacodynamic (PD) parameters of urinary glycolate and plasma glycolate • Evaluate growth parameters • Evaluate developmental milestones • Evaluate experiences of PH1 patients and/or caregivers during treatment with lumasiran • Assess for antidrug antibodies (ADA) against lumasiran	• Change from baseline in nephrocalcinosis as assessed by renal ultrasound • Change in frequency of renal stone events • Change in urinary glycolate and plasma glycolate • Change in growth parameters (z-scores) from baseline over time • Changes in developmental milestones over time • Changes in patient and/or caregiver experience as evaluated by a patient/caregiver survey • Frequency of ADA
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of AEs

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, PK, and PD of lumasiran in pediatric patients with PH1 who are younger than 6 years old and have relatively preserved renal function. All eligible patients will be administered open-label lumasiran; no control group will be assessed.

Patients will be screened from Day -60 to Day -1 to determine eligibility. Consented patients meeting eligibility criteria will receive their first dose of subcutaneously administered lumasiran on Day 1. Lumasiran will be administered SC utilizing weight-based dosing, with dose adjustments for interval weight gain, as specified in Section 5.2.2.

Patients will return to the clinical center for follow-up assessment of efficacy, safety, tolerability, PK, PD, and patient and caregiver experience and burden according to the schedule of assessments through the last study visit. Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, electrocardiograms (ECGs), physical examinations, and concomitant medications.

For all patients, single-void urine samples (in triplicate) will be collected during screening to establish baseline and then serially per the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4).

For patients able to provide 24-hour urine samples, three 24-hour urine collections will be scheduled during screening to establish baseline urinary oxalate levels. At Month 6, three 24-hour urine collections will be scheduled within 14 days prior to the Month 6 dose for patients who are able to provide 24-hour urine samples. For patients unable to provide 24-hour urine samples, a single catheterized collection may be requested.

This study will consist of 2 periods: a 6-month primary analysis period followed by a long-term extension period. During the 6-month primary analysis period, patients will undergo efficacy and safety assessments every 2 weeks for the first month and monthly thereafter. During the long-term extension period of up to 54 months, dosing will continue and visits will occur at least every-3-months.

Patients who discontinue study drug early will be asked to return for follow-up visits (see Section 4.3.1).

3.2. Duration of Treatment

The duration of treatment with lumasiran is up to 60 months.

3.3. Duration of Study

The estimated total time on study, inclusive of screening, for each patient is up to 62 months, including up to 2 months of screening followed by up to 60 months of treatment, with a month defined as 28 days.

3.3.1. Definition of End of Study for an Individual Patient

A patient is considered to have reached the end of the study if:

- the patient has completed the end of study (EOS; Month 60) visit, or
- the patient has completed the safety follow-up visits until PD recovery of urinary oxalate is >70% of baseline, and plasma glycolate is <30% above baseline or ≤ the ULN, or,
- the patient has completed 12 months of monitoring following the final lumasiran dose

3.4. Number of Planned Patients

The planned enrollment for this study is 20 patients including at least 1 patient <12 months of age with weight <10 kg at consent. Patients who discontinue study drug or stop participation in the study prior to Month 6 may be replaced (see Section 4.3.4), and the analysis of data collection prior to discontinuation is addressed in the statistical analysis plan.

3.5. Method of Assigning Patients to Treatment Groups

Patients will not be assigned to treatment groups. Dosing will be determined by the patient's weight (see Section 5.2.2).

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. Upon signing the informed consent form (ICF), the patient will be assigned a patient identification number by the interactive response system (IRS).

3.6. Blinding

While this is an open-label study, pharmacodynamic assessment data will not be distributed to the sites until after the patient has completed the Month 6 visit. Site personnel should refrain from obtaining or viewing local oxalate or glycolate assessments, except as medically indicated.

3.7. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will oversee the safety and overall conduct of this study, providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved by the DMC. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

Patients are eligible to be included in the study if all the following criteria apply:

Age

1. Have reached at least 37 weeks estimated gestational age (full-term infant) but less than 6 years of age at consent.

Patient and Disease Characteristics

2. Documentation of PH1 as determined by genetic analysis prior to initial dosing.
3. Urinary oxalate:creatinine ratio greater than the upper limit of normal based on age on at least 2 of 3 single-void collections during screening.
4. If taking therapeutic vitamin B6 (pyridoxine), must have been on stable regimen for at least 90 days before screening, and is able to remain on this stable regimen until at least the Month 6 visit. Dose adjustments for interval weight gain are acceptable.

Informed Consent

5. Legal guardian(s) is (are) willing and able to comply with the study requirements and to provide written informed consent; the patient should provide assent per local and national requirements.

4.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Laboratory Assessments

1. Has any of the following laboratory parameter assessments:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2× ULN for age during screening
   b. Total bilirubin >1.5×ULN during screening. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2× ULN
2. Has known active human immunodeficiency virus (HIV) infection, or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.
3. If ≥12 months old at screening, has an estimated glomerular filtration (GFR) of ≤45 mL/min/1.73m^2 (calculation will be based on the Schwartz Bedside Formula) at

screening; if <12 months old at screening, has serum creatinine value per the central laboratory above the ULN for age at screening.

Prior/Concomitant Therapy

4. Currently enrolled in another investigational drug study including the follow-up period, or less than 30 days or 5 half-lives (whichever is longer) since ending the drug study(s), or receiving other investigational agent(s).

Medical Conditions

5. Medical history includes clinical evidence of extrarenal systemic oxalosis as determined by the Investigator.
6. Has undergone renal or liver transplantation or a liver transplant is anticipated in the 6 months after the initial dose of lumasiran.
7. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
8. History of allergic reaction to an oligonucleotide or GalNAc.
9. History of intolerance to subcutaneous (SC) injection(s).

Contraception

10. For female patients who may achieve menarche during the study, is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.

4.3. Removal from Study Drug or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop protocol procedural assessments, or participation in the study as a whole at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may discontinue study drug or stop a patient's participation in the study at any time if this is considered to be in the patient's best interest. Any discontinuation of treatment or the stopping of the patient's participation in the study must be fully documented in the electronic case report form (eCRF) and should be followed up by the Investigator.

Discontinuation of study drug or declining procedural assessments is described in Section 4.3.1, while the stopping of a patient's participation in the study is detailed in Section 4.3.2.

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

Reasons for discontinuation of study drug include any of the following:

- Significant violation of the protocol
- AE
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up

- Other reason (non-AE)
- Or, study is terminated by the Sponsor

Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.6.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

Patients who discontinue study drug and/or decline procedural assessments should not be automatically removed from study. In general, patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses.

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4), including different options for follow-up and collection of data (eg, in person, by phone, by mail, through family or friends, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including SAEs, the event should be followed as described in Section 6.5.6. When a patient discontinues study drug dosing, the primary reason must be recorded in the electronic case report form (eCRF). Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month treatment period (defined as the time the first dose of study drug is administered on Study Day 1 through completion of the Month 6 assessments) will be encouraged to remain on the study and complete assessments (including 24-hour urine collections, but excluding PK assessments) through Month 6 (see Table 1). They will also be asked to complete safety follow-up visits, once every 3 months, per the safety follow-up schedule (see Table 3 or Table 4) for up to 12 months after the last dose of lumasiran, or until PD recovery (whichever is earlier).

Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete early termination (ET) assessments and complete safety follow-up visits, once every 3 months, per the safety follow-up schedule (see Table 3 or Table 4) for up to 12 months after the last dose of lumasiran, or until PD recovery (whichever is earlier).

PD recovery is defined as urinary oxalate >70% of baseline, and plasma glycolate <30% above baseline or ≤ the ULN (see Section 3.3.1).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient or Legal Guardian Stops Participation in the Study

A patient or their legal guardian may stop participation in the study at any time. A patient or legal guardian considering stopping participation in the study should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study to complete their study assessments, through the Month 6 visit, including follow-up, or

alternatively may complete any minimal assessments for which the patient or legal guardian consents as described in Section 4.3.1. If a patient or legal guardian still chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the 6-month treatment period, every effort should be made to conduct early the assessments scheduled to be performed at the Month 6 visit (see Table 1).

If the patient does not wish to or is unable to continue further study participation, the Investigator is to discuss with the patient appropriate procedures for stopping participation in the study. Data collected from the patient can continue to be used.

In addition, in the countries where the collection and processing of the patient data is based on the patient consent, if a patient withdraws consent to collect and process his/her data (see Section 4.3.2.2), as applicable, patient data up to the withdrawal of consent will be included in the analysis of the study. In addition, where permitted, publicly available data (such as appropriate national or regional vital status registry or other relevant databases) can be included after withdrawal of consent, where available and allowable by local law.

4.3.2.2. Withdrawal of Consent to Process the Patient's Personal Data

Where allowed by local law, the patient may decide to withdraw consent to collect, store, and use biological samples and, as applicable, other personal data, informing the study doctor at any time in writing or in any other form that may be locally required. The Sponsor will continue to keep and use the patient's study information (including any data resulting from the analysis of the patient's biological samples until the time of withdrawal) according to applicable law. The process for the storage and, as applicable, further use of remaining samples will be followed per local requirements.

4.3.2.3. Investigator or Sponsor Stops Participation of a Patient in the Study

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

Termination of the clinical study and site closure are described in Section 8.1.6.

4.3.2.4. Recording Reason for Stopping a Patient's Study Participation

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.6.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient misses a required study visit:

- The site must attempt to contact the patient or legal guardian and reschedule the missed visit as soon as possible and counsel the patient or legal guardian on the importance of maintaining the assigned visit schedule and ascertain if the patient or legal guardian wishes [for the patient] to continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient or legal guardian continue to be unreachable, the patient will be considered to have stopped participation in the study.
- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study prior to Month 6 may be replaced at the Sponsor's discretion, and the analysis of data collection prior to discontinuation is addressed in the statistical analysis plan. Patients who discontinue the study drug or stop participation in the study after Month 6 will not be replaced.

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed and returned unused must not be re-dispensed.

5.2. Study Drug

Detailed information describing the preparation, administration, and storage of lumasiran is provided in the Pharmacy Manual.

5.2.1. Description

Lumasiran will be supplied as a sterile solution in water for SC injection. See the Pharmacy Manual for further details of solution concentration and fill volume.

5.2.2. Dose and Administration

Patients will be administered lumasiran as an SC injection at the dose and regimen based on their weight category as described in Table 7. Patients will receive 3 loading doses, once monthly (at Day 1, Month 1, and Month 2) at a dose based on body weight category. At Month 3 and beyond, patients will receive lumasiran either monthly (patients weighing <10 kg) or every 3

months (patients weighing ≥10 kg) at the maintenance dose. For patients who are on a monthly dosing regimen, study drug administration must be at least 21 days apart.

Study drug injections will be administered under the supervision of the Investigator. The site of injection may be the abdomen, the upper arms or thighs. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be permitted at a location other than the study center (for example, the patient's home) by a healthcare professional with the oversight of the Investigator at all time points, provided the patient has tolerated at least 1 dose of lumasiran administered in the clinic. However, continued study drug administration at the study center should be considered for patients who have ongoing study drug-related AEs, worsening injection site reactions with repeat dosing, or for anyone in the opinion of the Investigator who would benefit from clinical observation following dosing.

If the patient is unable to come to the study site, and a visit by a healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, lumasiran may be administered by the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the caregiver must receive appropriate training on lumasiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes for dosing.

Table 7: Weight-based Dosing Regimen

Weight	Loading Dose (Day 1, Month 1, Month 2)	Maintenance Dose (Month 3 and Beyond)
<10 kg	6.0 mg/kg monthly for 3 months	3.0 mg/kg monthly
≥10 to <20 kg	6.0 mg/kg monthly for 3 months	6.0 mg/kg every 3 months
≥20 kg	3.0 mg/kg monthly for 3 months	3.0 mg/kg every 3 months

For patients who weigh <20 kg, the dose will be based on a weight obtained within 7 days prior to dosing. During periods of time when the COVID-19 pandemic impedes the ability of these patients to travel to the study site or healthcare professionals to go to patients' homes, a weight from up to 6 weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be used to calculate the amount of lumasiran to be administered.

For patients who weigh ≥20 kg, the dose may be based on a weight obtained up to 4 months prior to the planned quarterly dose.

Patients with weight increases crossing the threshold for the next weight-based dosing category (<10 kg to ≥10 kg or <20 kg to ≥20 kg) will follow the new dosing regimen for the remainder of the study or until the next dosing category threshold is reached (ie, patients will not switch back to the lower-weight dosing schedule if their body weight subsequently decreases).

Patients in maintenance dosing who transition from <10 kg to ≥10 kg will continue to receive monthly doses at 3.0 mg/kg until the next visit that coincides with Table 4, whereby they will follow every-3-months dosing as per Table 4 until the end of the study.

If a patient does not receive a dose of lumasiran within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

If a patient misses multiple consecutive doses, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see Section 4.3).

Patients whose disease progresses to requiring a dialysis regimen will continue on their planned dosing regimen prior to starting dialysis therapy. The lumasiran dose will be administered as soon as feasible following the end of dialysis, eg, within 2 hours of completing the dialysis session. If a patient does not receive a dose of lumasiran within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

Additional details can be found in the Pharmacy Manual. In addition, instructions and procedures related to administration of lumasiran by a caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

5.2.3. Dose Modifications

Dose modifications are not permitted.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

5.2.3.1. Liver Function Test Criteria for Withholding, Monitoring and Stopping Lumasiran Dosing

1. For patients who weigh <20 kg, liver function test (LFT) results (see Table 10) are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose of lumasiran. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes and LFT assessments are not feasible within 7 days prior to the dose, LFT test results up to 6 weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be reviewed to determine whether the dose can be administered.

   For patients who weigh ≥20 kg, LFT results may be reviewed up to 4 months prior to the planned quarterly dose to determine whether the dose can be administered.

2. Consult the Laboratory Manual for the blood draw priority list based on patient weight. Central laboratory results are preferable. If not available, local laboratory results may be used; however, if a local assessment is drawn, a serum chemistry sample must also be drawn for analysis at the central laboratory.

3. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 8.

4. For any ALT or AST elevation >3× ULN:
    a. If local laboratory results are obtained, confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. If an alternative cause is found, provide appropriate care.
    c. If an alternative cause is not found, perform assessments per Table 8 and Table 11.
5. For any ALT or AST elevation >3× ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or international normalized ratio (INR) ≥1.5, permanently discontinue dosing.
6. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 8:

Table 8: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 11 (all assessments to be performed; see Section 6.5.5.4 for guidance on maximal pediatric blood volumes)
	  • Hematology, serum chemistry, LFT per Table 10
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor at least every two weeks: LFT per Table 10
	• If elevation persists for ≥2 months, must discuss with the Medical Monitor before continuing dosing

>5× to 8× ULN	• Hold lumasiran dosing until recovery to ≤1.5× ULN or baseline; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 11 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT per Table 10
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor at least weekly: LFT per Table 10 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation by the central laboratory of the transaminase value

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function tests; ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center and the healthcare professional will be responsible for preparation of lumasiran doses, according to procedures detailed in the Pharmacy Manual. In cases where lumasiran is administered at home by a caregiver, dosing may be prepared and administered by the caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately [5±3°C].

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual and Patient/Caregiver Storage and Administration Instructions.

5.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

5.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs. Used, partially used, and unused study drug will be returned to the Sponsor (or designee) or destroyed at the clinical study center according to applicable regulations.

Further instructions about drug accountability will be detailed in the Pharmacy Manual.

5.3. Concomitant Medications and Procedures

Use of concomitant medications and procedures will be recorded on the patient's CRF as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). This includes all prescription medications, vaccines, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study must be recorded on the CRF. Patients should not start new medication regimens during the study, including regimens of vitamins or herbal medication, without consultation with the Investigator.

If patients use nonsteroidal anti-inflammatory drugs intermittently or chronically, they must have been able to tolerate them with no previous side effects (eg, gastric distress or bleeding).

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

If taking pyridoxine (vitamin B6) for the treatment of PH1, patients must have been on a stable regimen for at least 90 days before screening and remain on this stable regimen during the screening period and through at least the Month 6 visit. Dose adjustments for interval weight gain are permitted. Patients should avoid high dose vitamin C preparations within 4 days prior to oxalate assessments.

Patients may be treated for PH1 according to local standard of care. Patients should continue their current standard of care regimen, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy at least until the Month 6 visit. Standard of care treatment may be adjusted after Month 6 in accordance with clinical judgement. If pyridoxine therapy is discontinued, pyridoxine levels should be assessed for at least the next 2 timepoints indicated in the Schedules of Assessment. Consultation with the Medical Monitor is required if treated with any new emerging products.

For other permitted concomitant medications administered subcutaneously, do not administer in same injection site area as the study drug, for at least 7 days after the last dose of study drug.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the CRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

5.4. Treatment Compliance

Compliance with study drug administration will be verified by study staff.

5.5. Other Requirements

5.5.1. Contraception

Females who experience menarche during the course of the study should be asked to commit to true sexual abstinence for the remainder of their study participation and for 90 days after last dose administration. If a patient instead prefers to initiate contraception, the Investigator must approve the selected method.

Birth control methods which are considered highly effective include:

- Placement of an intrauterine device.
- Placement of an intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient).
- Established use of oral (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods, if they start heterosexual relationships during the study and for up to 90 days after the last dose of study drug.

Investigators should advise females of childbearing potential of the most appropriate birth control method available within their country taking into account local medical practice.

For male patients, no contraception is required. However, use by adolescent males of contraception (condom) may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient informed consent forms.

The Investigator will ensure that adolescent patients, and their legal representatives if applicable, are adequately informed about contraceptive requirements and the need for contraception once a patient initiates heterosexual intercourse. The need for contraception and compliance with

contraception requirements will be assessed at every visit for adolescent patients, and pregnancy testing will be performed before every dose for postmenarcheal females throughout the course of the study (see Section 6.5.5.2).

5.5.2. Dietary Restrictions

Patients should refrain from consumption of foods with high oxalate content, including, but not limited to, chocolate, rhubarb, spinach, and beet root, for 1 week prior to assessments of urinary and plasma oxalate.

6. STUDY ASSESSMENTS

The schedules of study assessments are provided in Table 1, Table 2, Table 3, and Table 4. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs, length/height and weight, abbreviated physical examination/body system assessment, and preparation and administration of study drug (at the discretion of the Investigator).

6.1. Screening Assessments

An informed consent form (ICF) that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the legal guardian (with patient assent, as applicable) before the Screening procedures are initiated. All legal guardians will be given a copy of the signed and dated ICF and assent form, as applicable.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. Rescreening of patients is permitted with consultation of the Medical Monitor (see Section 6.1.2).

Patient demographic data and medical history/disease history will be obtained. Non-serious events occurring after signing of the ICF and prior to study drug administration will be captured as medical history. Any changes to medical history occurring between the screening assessment and Day 1 will be updated prior to study drug administration.

A blood sample for *AGXT* mutation analysis will be collected during screening for patients who do not have documented PH1 genetic analysis to confirm eligibility.

If serum creatinine and liver function laboratory assessments are collected greater than 30 days prior to Day 1, repeat the assessment and review results prior to initial dosing.

For all patients, single-void urine samples (in triplicate) will be collected during screening to establish baseline. In addition, for patients able to provide 24-hour urine samples, three 24-hour urine collections will be scheduled during screening to establish baseline urinary oxalate levels. 24-hour urine collections are the preferred method of evaluating urinary oxalate levels and patients are strongly encouraged to complete these collections during supervised visits unless their legal guardians are already familiar with the collection procedures. For patients unable to

provide 24-hour urine samples, a single catheterized collection will be obtained, when allowed, during screening.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests, excluding urinary oxalate, may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during Screening provided that the patient can be evaluated for eligibility and randomized within the allowed Screening period.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria due to a transient condition observed at Screening (eg, prohibited medications that were subsequently discontinued) may be allowed to return for rescreening after consultation with the Medical Monitor. The legal guardian will be re-consented, and assent obtained (if applicable) if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

24-hour urine collections are the preferred method of evaluating urinary oxalate levels. Since not all patients will be able to provide 24-hour urine samples, single-void urine samples (in triplicate) will be collected throughout the study in all patients. Table 9 shows the 24-hour urine collection procedure by study visit.

In children who are able to comply with 24-hour urine collection procedures, urinary oxalate excretion will be determined from 24-hour urine sample collections to be completed at the time points specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). Urinary oxalate concentrations will be analyzed centrally using a validated assay. Non-catheterized 24-hour urine collections must meet pre-specified validity criteria (see Section 6.2.1.1). The duration of collection and volume of urine in the collection will be recorded in the eCRF.

For patients who are able to comply with the 24-hour urine collection procedure, three 24-hour urine collections will be scheduled during screening to establish baseline urinary oxalate excretion. For Month 6, three 24-hour urine collections will be scheduled within 14 days prior to the Month 6 dose to evaluate changes in oxalate concentrations over the first 6-month interval. A single 24-hour collection will be scheduled at Month 12 and then every 6 months thereafter.

Patients able to comply with 24-hour urine collections will either bring a 24-hour urine collection to the clinic, courier samples to the laboratory, or have their 24-hour urine collected during an inpatient stay at the time of the study visit.

For patients who are unable to comply with 24-hour urine collections, a single catheterized 24-hour collection will be obtained, when allowed, at both baseline and Month 6. Catheterized collections may be performed at the discretion of the Investigator and with the consent of the legal guardian. Catheterized collections will be considered complete if there is no documented urine loss during the collection.

All patients will have triplicate single-void samples collected within 7 days prior to dosing, as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4); and either single or triplicate collections within 7 days prior to dosing as specified in the Schedules of Assessment (see Table 3 or Table 4). First morning voids are the preferred sample, when feasible. Samples may be collected as an outpatient prior to the visit or collected during the study visit prior to dosing, as applicable.

Table 9: 24-hour Urine Collection Procedure by Study Visit

Study Visit and 24-hour Urine Collection Window	Number of 24-hour Collections	Notes
Screening (within 60-day period prior to initial dosing)	3 voided collections or 1 catheterized collection (when allowed)	Supervised 24-hour collections are encouraged unless patient/caregiver already familiar with collection procedure.
Month 6 (within 14 days prior to dosing)	3 voided collections or 1 catheterized collection (when allowed)	Supervised 24-hour collections are encouraged unless patient/caregiver already familiar with collection procedure.
Month 12 and Every 6 Months Through End of Study	1 voided collection	--

6.2.1.1. Validity Criteria for Non-catheterized 24-hour Urine Collections

A urine collection will be considered valid if each of the following criteria are met:

- The collection is between 18-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection.
- The 24-hour creatinine content is at least 5 mg/kg as assessed by the study central lab.

6.3. Pharmacodynamic and Renal Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma and urinary oxalate and glycolate concentrations) and renal parameters at the time points specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). All blood and urine samples will be collected prior to dosing, if applicable. Optional collections may be performed at the discretion of the Investigator.

All PD assessments will be analyzed centrally. Pharmacodynamic assessment data will not be distributed to the sites until after the patient has completed the Month 6 visit. Site personnel should refrain from obtaining or viewing local oxalate or glycolate assessments, except as

medically indicated. Details regarding the processing and aliquoting of samples for storage and analyses will be provided in the Laboratory Manual.

Where local regulations allow, and infrastructure is in place, home nursing may be used to collect urine and blood samples.

6.3.1. Urinary Oxalate:Creatinine Ratio

Urine oxalate:creatinine ratios will be calculated from the oxalate and creatinine levels measured in the 24-hour urine collections to assess the PD effect of lumasiran on urinary oxalate:creatinine ratio. Urinary oxalate:creatinine ratios from single-void urine collections will also be measured.

6.3.2. Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR will be obtained at the time points specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). eGFR (mL/min/1.73 m^2) will be calculated in patients ≥12 months of age at the time of the assessment to evaluate renal function during the study. The calculation will be based on the Schwartz Bedside Formula (Appendix 10.1).[Levey 2009; Schwartz 2009]

6.3.3. Renal Stone Events

A renal stone event is defined as an event which includes at least one of the following:

- Visit to healthcare provider (eg, outpatient clinic, urgent care, emergency department, procedure) because of a renal stone
- Medication for renal colic
- Stone passage
- Macroscopic hematuria due to a renal stone

All relevant clinical information pertaining to the event should be obtained, including laboratory values, medical records, discharge summaries, and medical test results.

Since renal stone events are recorded as an efficacy assessment for lumasiran, these will not be treated as AEs or SAEs. However, if a patient experiences other AEs or SAEs during a renal stone event, they should be reported (see Section 6.5.6.1).

6.3.4. Renal Ultrasound

Renal ultrasounds will be obtained locally, at the timepoints specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, renal ultrasounds may be completed up to 3 months after the intended timepoint for assessments scheduled prior to Month 12, and up to 9 months after the intended timepoint for visits at Month 12 and later. Renal ultrasound will be performed according to instructions provided in the Study Manual in a standardized manner. Renal ultrasounds will be reviewed centrally.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for assessment of lumasiran PK parameters and possible metabolite analysis (as necessary) at the time points in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4).

Plasma PK parameters, maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F), will be calculated for the lumasiran plasma concentration profiles. A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 5. In addition, if an SAE occurs associated with dosing, an additional PK sample may be collected at 4 to 8 hours postdose on the day of dosing, where blood volume permits (see Section 6.5.5.4).

Lumasiran plasma concentrations will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs, including SAEs, recording of concomitant medication and measurements of vital signs, weight and height/length, ECG findings, and laboratory tests. Clinically significant abnormalities observed during the physical examination will be recorded.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4) and include blood pressure, heart rate, body temperature, and respiratory rate. On dosing days, vital signs will be measured predose. On Day 1 only, vital signs will also be measured 30 ± 10 minutes postdose. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn, where possible.

Vital signs should be measured after the patient has rested comfortably for 10 minutes, when feasible. Blood pressure should be taken using the same limb, when feasible. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Additional vital sign assessments, as medically indicated, may be added at the discretion of the Investigator, or as per DMC advice.

Vital signs results will be recorded in the eCRF.

6.5.2. Weight and Height/Length

Height/length will be measured in centimeters. Standing height should be captured for patients ≥24 months old who are able to stand independently. Supine length should be captured for patients <24 months old or those unable to stand independently. All height/length measurements should be performed in triplicate. Body weight will be measured in kilograms. Height and body

weight measurements will be collected as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4) and in Section 5.2.2; measurements will be recorded in the eCRF.

6.5.3. Physical Examination

Full and abbreviated physical examinations will be conducted according to the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). If a physical examination is scheduled for a dosing visit, it should be conducted prior to dosing. Full physical examinations will include the examination of the following: general appearance; head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid; lymph nodes; and neurological status.

Abbreviated physical examinations (body system assessment) will include examination of at least the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

If a visit is conducted offsite (eg, at the patient's home), a body system assessment may be performed in lieu of a physical examination.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE eCRF as appropriate.

6.5.4. Electrocardiogram

Single 12-lead ECGs will be obtained predose, when applicable, at the timepoints specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, ECG assessments may be completed up to 3 months after the intended timepoint for assessments scheduled prior to Month 12, and up to 9 months after the intended timepoint for visits at Month 12 and later. 12-lead ECGs will be locally read.

When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn and when the patient is calm.

The Investigator or qualified designee will review all ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. These assessments will be recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator, or as per DMC advice. Recordings will be archived according to the Study Manual.

6.5.5. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory, except in cases where it is not feasible to perform all tests centrally due to blood draw volume limits, ie, in infants and very young patients, hematology, and biochemistry panels may be performed locally, with central laboratory confirmation of any abnormalities. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation

may be requested. Clinical laboratory assessments are listed in Table 10 and will be assessed as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the visit assessments, all laboratory assessments specified in Table 10 which are performed at a local laboratory should also be sent in parallel to the central laboratory. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results on samples drawn on the same day.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and should be included in the clinical database.

Consult the Laboratory Manual for the blood draw priority list based on patient weight (see Section 6.5.5.4).

Clinical laboratory assessments may be collected at the clinical site or at a location other than the clinical study center by a trained healthcare professional.

Table 10: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Uric acid	Albumin
Total protein	Calcium
Glucose	Carbon dioxide
Creatinine and eGFR (using Bedside Schwartz formula for children ≥12 months at assessment)	Chloride
Pyridoxine (vitamin B6)[a]	
Liver Function Tests	
AST	ALP
ALT	Serum bilirubin (total and direct)
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin (optional)	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	

Abbreviations: ALP=alkaline phosphatase; ALT= alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; PH1=primary hyperoxaluria type 1; RBC=red blood cell

[a] Pyridoxine (vitamin B6) is required through Month 12 and only for patients receiving vitamin B6 for the treatment of PH1. On days when a blood sample for pyridoxine will be collected, patients should be instructed not to take vitamin B6 within 6 hours prior to blood sample collection.

6.5.5.1. Immunogenicity

Blood samples will be collected to evaluate antidrug antibodies. Blood samples for antidrug antibody testing must be collected before study drug administration as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). A blood sample to evaluate antidrug antibodies will be collected at the Early Termination visit, if applicable.

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.5.5.2. Pregnancy Testing

A pregnancy test will be performed for pediatric/adolescent females upon initiation of menarche. A serum pregnancy test will be performed at the first visit after menarche and urine pregnancy tests will be performed thereafter per the Schedule of Assessment and any time pregnancy is suspected. Pregnancy testing may be performed offsite by a caregiver if a caregiver will be administering study drug. More frequent pregnancy testing may be performed where required per local requirements. The results of the pregnancy test must be known before study drug administration. Patients who become pregnant are not eligible for continued study drug treatment. Any female with a positive pregnancy test during the study will be discontinued from study drug but will continue to be followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

6.5.5.3. Additional Liver Function Assessments

LFT results should be reviewed prior to dosing as described in Section 5.2.3.1.

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.3.1. Consult the Laboratory Manual for the blood draw priority list based on patient weight.

Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, and as per the blood draw priority list, all assessments in Table 11 will be performed one time, as well as hematology, serum chemistry, and LFT assessments from Table 10, and other assessments or evaluations per Investigator discretion, as appropriate. See Section 6.5.5.4 for the maximum blood volumes that can be collected from pediatric patients in this study.

Monitoring and dose modification will also be performed as outlined in Section 5.2.3.1.

Table 11: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
HBsAg, HBc antibody IgM and IgG	Parvovirus B19
HAV antibody IgM	HHV-6
HCV antibody	Anti-nuclear antibodies
HCV RNA PCR – qualitative and quantitative	Anti-smooth muscle antibodies
HEV antibody IgM	Anti-LKM1 antibody
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Anti-mitochondrial antibodies
Herpes Zoster Virus IgM, IgG	Anti-SLA
Epstein-Barr Virus antibodies, IgM and IgG	Ferritin
Cytomegalovirus antibodies, IgM, IgG	Ceruloplasmin
Imaging	
Abdominal ultrasound with Doppler flow (or CT or MRI) including right upper quadrant	
Focused Medical and Travel History	
Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	Alcohol consumption and drugs of abuse
Other potentially hepatotoxic agents including any work-related exposures	Recent travels to areas where hepatitis A or E is endemic

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid; SLA=soluble liver antigen.
Note:

- All assessments will be measured in central laboratory or locally when not feasible to conduct centrally, ie, due to blood volume restrictions. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed. Assessments can be staggered due to blood volume limitations (see Section 6.5.5.4).

6.5.5.4. Maximum Blood Volume

The maximum blood volume, which will be collected from pediatric patients over the course of the study, will be based on age and weight and will not exceed those specified in Table 12 from the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document (see Appendix Section 10.2).[Feinstein_Institute 2013] Consult the Laboratory Manual for the blood draw priority list based on patient weight.

6.5.6. Adverse Events

6.5.6.1. Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Renal stone events (as defined in Section 6.3.3) are recorded for efficacy assessment of lumasiran. These events will not be treated as AEs or SAEs. Other AEs or SAEs occurring during a renal stone event are reported.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event which places the patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above (eg, events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse).

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN)
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of study drug.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the

injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

For information on recording and reporting of AEs of clinical interest, see Section 6.5.6.2 and Section 6.5.6.3, respectively.

Adverse Event Severity

AEs are to be graded according to the categories detailed below:

Mild:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate:	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Severe:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden); OR life-threatening consequences; urgent intervention indicated; OR death related to an AE.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAE).

Relationship of the Adverse Event to Study Drug

The relationship of each AE to study drug should be evaluated by the Investigator by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" A "yes" response indicates that the event is considered as related to the study drug.

6.5.6.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient or legal guardian should be asked about medically relevant changes in the patient's health since the last visit. The patient or legal guardian should also be asked if the patient has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, ECG changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to study drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) on both the eCRF and the SAE form.

For AEs that are considered AEs of clinical interest (see Section 6.5.6.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to CRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reaction Signs or Symptoms eCRF, recording additional information regarding each injection site reaction that is entered on the AE eCRF (eg, symptom(s), injection site location, follow-up actions taken, etc.).

6.5.6.3. Reporting Adverse Events of Clinical Interest to Sponsor/Designee

For AEs that are considered AEs of clinical interest (see Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF.

6.5.6.4. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 6.5.6.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and the SAE form. SAEs must be reported using the contact information provided in the Study Manual.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

6.5.6.5. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative will report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

6.5.6.6. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

6.5.6.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through study completion, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy, the possible effects on the fetus, and be counseled to not breastfeed for 90 days after the last dose of study drug.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 6.5.6.4.

6.5.6.8. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol for the patient's weight category. The Investigator will decide whether a dose is to be considered an overdose, in consultation with the Sponsor. In the event of an overdose, the actual dose administered must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

6.5.7. COVID-19 Data Collection

Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

6.6. Biomarkers, DNA Genotyping, and Biospecimen Repository

Alnylam's RNAi therapeutics platform permits the highly specific targeting of investigational therapies based on genetic sequence. It is possible that variations in the target genetic sequence will result in variations in drug effect. More generally, genetic variations may account for the well-described heterogeneous manifestations of disease in patients with PH1, as well as their responses to treatment.

Where allowed per local regulations, ethics committee (IRB/IEC) approval, and legal guardian consent (and patient assent, where applicable), samples will be collected as part of this study to permit exploratory investigations and the application of novel approaches to bioanalyses that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action, and/or efficacy of lumasiran.

Biological specimens will be collected at the intervals indicated in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). Potential exploratory investigations may include DNA, RNA, or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

The biospecimen repository will also include residual material from routine samples (safety laboratory samples, PK samples, etc.) that are obtained during the study.

These specimens will be securely stored in a central biorepository for up to 10 years following the completion of this clinical study (ie, last patient last visit), or as per local regulations. After 10 years have elapsed, samples will be destroyed.

Details regarding the collection, processing, storage, and shipping of the samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by Alnylam Pharmaceuticals or its designees.

When biobanking is permitted by local regulation, study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

6.7. Developmental Assessments

The Vineland Adaptive Behavior Scale will be assessed at the timepoints specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4), and may be completed up to 4 months after the intended time point during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, to assess the achievement of developmental milestones over time. This tool assesses the domains of communication, daily living skills, socialization, and motor skills. The survey can be completed in 20-60 minutes.

6.8. Patient/Caregiver Experience and Impact Questionnaire

The patient/caregiver experience and impact questionnaire will be used to assess the experiences of patients living with PH1 and their caregivers, including the impact of the disease on their lives with respect to their need to relocate/travel for treatment, and the number and type of healthcare providers they use. The questionnaire will also assess the impact on patients' education and caregivers' employment and education, as applicable. This questionnaire will be completed by the caregiver (reporting on behalf of the patient for patient experience items) at the time points specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4) when feasible, and may be completed up to 4 months after the intended time point during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol. For information on study endpoints, see Section 2.

7.1. Determination of Sample Size

The planned enrollment for the study is 20 patients. The sample size was determined based on feasibility considerations, not power calculations.

7.2. Statistical Methodology

Statistical analyses will be primarily descriptive in nature.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) will be presented. For continuous variables, descriptive statistics will be presented (ie, number of patients, mean, median, standard deviation, standard error, minimum and maximum values).

All data will be provided in by-patient listings. Additional data summaries to help understand any impact of COVID-19 on efficacy and safety assessments will be outlined in the SAP.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- Safety Analysis Set: All patients who received any amount of study drug will be grouped according to the treatment actually received.

- Efficacy Analysis Set: All patients who received any amount of lumasiran and have at least one valid spot urinary oxalate:creatinine ratio value at baseline and at least one valid spot urinary oxalate:creatinine ratio value from assessment(s) at Month 3 to Month 6.
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.

The Safety Analysis Set will be used for safety analyses and sensitivity analysis of efficacy. The Efficacy Analysis Set will be used to evaluate efficacy endpoints. The PK Analysis Sets will be used to conduct PK analyses.

7.2.2. Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized for the Safety Analysis Set.

7.2.5. Efficacy Analyses

The analysis of the efficacy endpoints will be based upon the Efficacy Analysis Population. Descriptive summaries will be provided for the primary endpoint percent change in urinary oxalate excretion from baseline to Month 6. The analysis will be performed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in spot urine oxalate:creatinine ratio. The model includes baseline value as covariate and fixed effect terms including treatment arm and visit (Months 3, 4, 5, 6). The treatment estimates from this model will represent an average percent change from baseline of spot urine oxalate:creatinine ratio across Month 3 through Month 6 at which the treatment effect is expected to have reached steady state. Furthermore, given the variability of spot oxalate:creatinine ratio, averaging the values across these visits will yield stable treatment estimates. Sensitivity analyses will be conducted to assess the robustness of the estimates and will be detailed in the SAP. In addition, descriptive statistics scheduled visit will be presented and by-patient listings and figures will be generated displaying all assessments (scheduled and unscheduled).

Secondary efficacy and exploratory endpoints which are continuous will be summarized descriptively in the same manner as described above. For binary endpoints, the number and percentages of patients in each category will be displayed at each visit.

7.2.6. Pharmacodynamic Analysis

Urinary oxalate and glycolate excretion, urinary oxalate:creatinine ratio and plasma levels of oxalate and glycolate will be summarized over time for all patients in the Efficacy Analysis Set.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods.

Pharmacokinetic parameters include, but will not be limited to: C_{max}, t_{max}, $t_{½\beta}$, AUC, CL/F, and V/F. Other parameters may be calculated, if deemed necessary.

7.2.8. Safety Analyses

The main parameter is the frequency of treatment-emergent AEs (hereafter referred to simply as AEs). Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. Extent of exposure will be summarized overall.

Prior and concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary. Results will be tabulated by Anatomical Therapeutic Chemical (ATC) Classification System and Preferred Term (PT).

AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) overall. AEs, SAEs, related AEs, and AEs leading to discontinuation will be summarized by System Organ Class (SOC) and PT for each treatment arm. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data, ECG, and vital signs data. Laboratory shift tables from baseline to worst values will be presented.

Other safety summaries will be presented as appropriate. Further details will be specified in the SAP.

7.2.9. Immunogenicity Analyses

Antidrug antibody results will be summarized descriptively by patient and overall.

7.2.10. Interim Analysis

There may be interim analyses performed to support regulatory and/or publications requests.

7.2.11. Optional Additional Research

Optional additional research may be conducted in the future on the biological samples and/or data collected during the study in accordance with the strict terms of the informed consent form (see Section 4.3.2).

8. STUDY ADMINISTRATION

8.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

8.1.1. Informed Consent

The Investigator will ensure that the patient or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The patient or their legal guardian must also be notified that they are free to discontinue from the study at any time. The patient or legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided. Legal guardian(s) must provide informed consent and the patient should provide assent per local regulations and institutional standards.

The patient's or legal guardian's signed and dated informed consent (or assent, if applicable) must be obtained before conducting any study tests or procedures that are not part of routine care.

When a patient under the age of legal consent who has been enrolled in the study reaches the legal age of consent, the Investigator must obtain the patient's informed consent or assent, as applicable, prior to performing any further research interventions and/or procedures involving that patient per local regulations and institutional standards.

The Investigator must maintain the original, signed ICF (assent form, if applicable). A copy of the signed ICF (assent form, if applicable) must be given to the patient or legal guardian.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

8.1.2. Ethical Review

The study protocol, including the ICF (assent form, if applicable), must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all patient materials for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the legal guardian consent form and patient assent form, as applicable per institutional standards and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 6.5.6. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

Any communications from regulatory agencies, IRBs, or IECs in regard to inspections, other studies that impact this protocol or the qualifications of study personnel should be promptly reported to the Sponsor or its designee.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor or designee will provide this information to the Investigator.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and the IRB or IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB or IEC and the Regulatory Authority for approval before patients are enrolled under the amended protocol, and legal guardians must be re-consented to the most current version of the ICF (and patient assent form, as applicable).

8.1.3. Serious Breach of Protocol

Investigators must notify the Medical Monitor within 24 hours of becoming aware of a potential serious breach of the protocol. A serious breach is a breach that is likely to affect to a significant degree the safety and rights of a study participant or the reliability and robustness of the data generated in the clinical trial.

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory or as locally required, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

To comply with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

8.1.5. End of Study

The end of study is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant this action may include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients participating in the study
- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- The decision on the part of the Sponsor to suspend or discontinue treatment with the study drug

Should the study be terminated, and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up.

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

Study data must be recorded on CRFs (paper and/or electronic) provided by the Sponsor or designee on behalf of the Sponsor. Case report forms must be completed only by persons designated by the Investigator. If eCRFs are used, study data must be entered by trained site personnel with access to a valid and secure eCRF system. All data entered into the eCRF must also be available in the source documents. Corrections on paper CRFs must be made so as to not obliterate the original data and must be initialed and dated by the person who made the correction.

8.2.2. Study Monitoring

The Monitor, as a representative of the Sponsor, has an obligation to closely follow the study conduct at the site. The Monitor will visit the Investigator and clinical study center periodically and will maintain frequent telephone and written contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

The Monitor will review source documents, systems and CRFs to ensure overall quality and completeness of the data and to confirm study procedures are complied with the requirements in the study protocol accurately. The Sponsor, or its designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, site standard operating procedures and training records, and other records relative to study conduct.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the

protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published or following the period of 12 months after completion of the study at all centers. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement among the institution, Investigator, and Alnylam will detail the procedures for Alnylam's review of publications.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

9. LIST OF REFERENCES

Al-Eisa AA, Samhan M,Naseef M. End-stage renal disease in Kuwaiti children: an 8-year experience. Transplant Proc. 2004 Jul-Aug;36(6):1788-91.

Boualla L, Tajir M, Oulahiane N, Lyahyai J, Laarabi FZ, Chafai Elalaoui S, et al. AGXT Gene Mutations and Prevalence of Primary Hyperoxaluria Type 1 in Moroccan Population. Genet Test Mol Biomarkers. 2015 Sep 18.

Cochat P,Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013 Aug 15;369(7):649-58.

Danpure CJ. Primary Hyperoxaluria. In: Beaudet AL, editor. The Online Metabolic and Molecular Bases of Inherited Disease. New York, NY: The McGraw-Hill Companies, Inc.; 2014.

Feinstein_Institute. The Feinstein Institute for Medical Research. Human Subject Protection Program Guidance Document: Maximum Blood Draw Limits. http://www.feinsteininstitute.org/wp-content/uploads/2013/02/Maximum-Blood-Draw-Limits.pdf. 2013.

Frishberg Y, Rinat C, Shalata A, Khatib I, Feinstein S, Becker-Cohen R, et al. Intra-familial clinical heterogeneity: absence of genotype-phenotype correlation in primary hyperoxaluria type 1 in Israel. Am J Nephrol. 2005 May-Jun;25(3):269-75.

Harambat J, Fargue S, Acquaviva C, Gagnadoux MF, Janssen F, Liutkus A, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. Kidney Int. 2010 Mar;77(5):443-9.

Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. J Am Soc Nephrol. 2015 Feb 2.

Hoppe B. Evidence of true genotype-phenotype correlation in primary hyperoxaluria type 1. Kidney Int. 2010 Mar;77(5):383-5.

Hoppe B, Danpure CJ, Rumsby G, Fryer P, Jennings PR, Blau N, et al. A vertical (pseudodominant) pattern of inheritance in the autosomal recessive disease primary hyperoxaluria type 1: lack of relationship between genotype, enzymic phenotype, and disease severity. Am J Kidney Dis. 1997 Jan;29(1):36-44.

Johnson TN, Tucker GT, Tanner MS,Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. Liver Transpl. 2005 Dec;11(12):1481-93.

Kamoun A,Lakhoua R. End-stage renal disease of the Tunisian child: epidemiology, etiologies, and outcome. Pediatr Nephrol. 1996 Aug;10(4):479-82.

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002 May(246):1-190.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

Liebow A, Li X, Racie T, Hettinger J, Bettencourt BR, Najafian N, et al. An Investigational RNAi Therapeutic Targeting Glycolate Oxidase Reduces Oxalate Production in Models of Primary Hyperoxaluria. J Am Soc Nephrol. 2017 Feb;28(2):494-503.

Lieske JC, Monico CG, Holmes WS, Bergstralh EJ, Slezak JM, Rohlinger AL, et al. International registry for primary hyperoxaluria. Am J Nephrol. 2005 May-Jun;25(3):290-6.

Mandrile G, van Woerden CS, Berchialla P, Beck BB, Acquaviva Bourdain C, Hulton SA, et al. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. Kidney Int. 2014 Dec;86(6):1197-204.

National Centers for Health Statistics. The National Health and Nutrition Examination Survey (NHANES). CDC; 2018 [updated 31 July 2018; cited 2018]; program of studies designed to assess the health and nutritional status of adults and children in the United States]. Available from: https://www.cdc.gov/nchs/nhanes/index.htm.

Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-37.

van der Hoeven SM, van Woerden CS,Groothoff JW. Primary hyperoxaluria type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort. Nephrol Dial Transplant. 2012 Oct;27(10):3855-62.

van Woerden CS, Groothoff JW, Wanders RJ, Davin JC,Wijburg FA. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. Nephrol Dial Transplant. 2003 Feb;18(2):273-9.

Williams EL, Acquaviva C, Amoroso A, Chevalier F, Coulter-Mackie M, Monico CG, et al. Primary hyperoxaluria type 1: update and additional mutation analysis of the AGXT gene. Hum Mutat. 2009 Jun;30(6):910-7.

10. APPENDICES

10.1. Formulae for Estimated Glomerular Filtration Rate Calculation

Estimated glomerular filtration rate (eGFR; in mL/min/1.73m^2) will be calculated from serum creatinine (SCr) based on the Schwartz Bedside Formula for patients ≥12 months of age at the time of assessment.

Schwartz Bedside Formula [Schwartz 2009]

- Conventional units
  - eGFR (mL/min/1.73 m^2) = (0.413 × height [cm])/SCr (mg/dL)
- SI units
  - eGFR (mL/min/1.73 m^2) = (36.2 × height [cm])/SCr (µmol/L)

10.2. Blood Volume Limits in Pediatric Patients

The maximum blood volume, which will be collected from pediatric patients over the course of the study, will be based on age and weight and will not exceed those specified in Table 12, which was adapted from the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document.

Table 12: Maximum Allowable Total Blood Volume Collection Chart

Body Weight	Body Weight	Total Blood Volume	Maximum Allowable Volume in a 24-hour Period		Total Volume Collected in a 30-day Period	
			2.5% of total blood volume	3% of total blood volume	5% of total blood volume	10% of total blood volume
(kg)	(lbs)	(mL)	(mL)	(mL)	(mL)	(mL)
1	2.2	100	2.5	3	5	10
2	4.4	200	5	6	10	20
3	6.6	240	6	7.2	12	24
4	8.8	320	8	9.6	16	32
5	11	400	10	12	20	40
6	13.2	480	12	14.4	24	48
7	15.4	560	14	16.8	28	56
8	17.6	640	16	19.2	32	64
9	19.8	720	18	21.6	36	72
10	22	800	20	24	40	80
11-15	24-33	880-1200	22-30	26.4-36	44-60	88-120
16-20	35-44	1280-1600	32-40	38.4-48	64-80	128-160
21-25	46-55	1680-2000	42-50	50.4-60	64-100	168-200
26-30	57-66	2080-2400	52-60	62.4-72	104-120	208-240
31-35	68-77	2480-2800	62-70	74.4-84	124-140	248-280
36-40	79-88	2880-3200	72-80	86.4-96	144-160	288-320
41-45	90-99	3280-3600	82-90	98.4-108	164-180	328-360
46-50	101-110	3680-4000	92-100	110.4-120	184-200	368-400
51-55	112-121	4080-4400	102-110	122.4-132	204-220	408-440
56-60	123-132	4480-4800	112-120	134.4-144	224-240	448-480
61-65	134-143	4880-5200	122-130	146.4-156	244-260	488-520
66-70	145-154	5280-5600	132-140	158.4-168	264-280	528-560
71-75	156-165	5680-6000	142-150	170.4-180	284-300	568-600
76-80	167-176	6080-6400	152-160	182.4-192	304-360	608-640
81-85	178-187	6480-6800	162-170	194.4-204	324-340	648-680
86-90	189-198	6880-7200	172-180	206.4-216	344-360	688-720
91-95	200-209	7280-7600	182-190	218.4-228	364-380	728-760
96-100	211-220	7680-8000	192-200	230.4-240	384-400	768-800

Adapted from http://www.feinsteininstitute.org/wp-content/uploads/2013/02/Maximum-Blood-Draw-Limits.pdf.[Feinstein_Institute 2013]

ALN-GO1-004 PROTOCOL AMENDMENT 1.0 SUMMARY OF CHANGES DATED 09 AUGUST 2019

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

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to increase the sample size of the study due to a lower than expected screening failure rate, and to align clinical objectives and endpoints across the Phase 3 program by shifting the evaluation of the effect of lumasiran on plasma oxalate from an exploratory objective to a secondary objective. Several additional changes are being implemented as outlined below.

An additional secondary endpoint for the Extension Phase of the study has been added to evaluate the effects of lumasiran on the duration of urinary oxalate reduction:

- Percentage of time that spot urinary oxalate:creatinine ratio is at or below the near-normalization threshold (≤1.5 × ULN)

Clarifications have been added for the following:

- Clarify that although the study is open-label, pharmacodynamic assessment data should not be distributed to sites until the patient has completed Month 6
- Clarify that additional liver function tests are to be performed when no alternative cause of elevated transaminases is identified
- Clarify that specific study assessments may be conducted at a location other than the study center by a home healthcare professional
- Clarify that specific laboratory tests may be performed locally in cases where it is not feasible to perform laboratory tests centrally, with central confirmation of any laboratory abnormalities

In addition to these changes, the following have been implemented for this study:

- Added study drug dosing instructions for patients whose disease progresses to requiring a dialysis regimen during the study
- Updated the description of the analysis populations and included description of the efficacy statisticial analysis methods

A detailed summary of changes is provided in Table 1. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 1.0 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Protocol Amendment X are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Description: Added an additional endpoint for the evaluation of the effects of lumasiran on additional measures of urinary oxalate, and changed the evaluation of lumasiran on plasma oxalate levels from exploratory to secondary objectives and endpoints

The primary change occurs in Section 2, Objectives and Endpoint

Now reads:

Objectives	Endpoints
Primary	
• Evaluate the effect of lumasiran on urinary oxalate excretion	• Percent change in urinary oxalate excretion from baseline to Month 6
Secondary	
Extension Phase (Month 6 to End of Study) • Evaluate the long-term effects of lumasiran on urinary oxalate	Extension Phase (Month 6 to End of Study) • Percent change in urinary oxalate excretion from baseline • **Percentage of time that spot urinary oxalate:creatinine ratio is at or below the near-normalization threshold (≤1.5 × ULN)**
Duration of Study • Evaluate the effects of lumasiran on additional measures of urinary oxalate • **Evaluate the effects of lumasiran on plasma oxalate** • Characterize the pharmacokinetics (PK) of lumasiran • Evaluate the effect of lumasiran on renal function	Duration of Study • Absolute change in urinary oxalate excretion from baseline • Proportion of patients with urinary oxalate excretion ≤ the upper limit of normal (ULN) and ≤ 1.5 x ULN • **Change (percent and absolute) in plasma oxalate from baseline** • Plasma PK parameters of lumasiran • Change from baseline in estimated glomerular filtration rate (eGFR)
Exploratory	
• Evaluate effect of lumasiran on nephrocalcinosis • Evaluate the effect of lumasiran on the occurrence of renal stones • Evaluate the additional pharmacodynamic (PD) parameters of urinary glycolate **and** plasma glycolate~~, and plasma oxalate~~ • Evaluate growth parameters • Evaluate developmental milestones • Evaluate experiences of PH1 patients and/or caregivers during treatment with lumasiran • Assess for antidrug antibodies (ADA) against lumasiran	• Change from baseline in nephrocalcinosis as assessed by renal ultrasound • Change in frequency of renal stone events • Change in urinary glycolate **and** plasma glycolate~~, and plasma oxalate~~ • Change in growth parameters (z-scores) from baseline over time • Changes in developmental milestones over time • Changes in patient and/or caregiver experience as evaluated by a patient/caregiver survey • Frequency of ADA
Safety	

Objectives	Endpoints
• To evaluate the safety and tolerability of lumasiran	• Frequency of AEs

Sections also containing this change:

- Protocol Synopsis

Description: Updated the study sample size and referred to statistical analysis plan for analysis details

The primary change occurs in Section 3.4, Number of Planned Patients

Now reads: The planned enrollment for this study is **~~up to~~ 20** ~~8~~ patients**,** including **at least** ~~4 patients ≥12 months of age at screening, and~~ 1 patient <12 months of age with weight <10 kg at consent. Patients who discontinue study drug or stop participation in the study prior to Month 6 may be replaced (see Section 4.3.4)**, and the analysis of data collection prior to discontinuation is addressed in the statistical analysis plan**.

Sections also containing this change:

- Protocol Synopsis
- Section 7.1, Determination of Sample Size
- Section 4.3.4, Replacement of Study Patients

Description: Clarify that while the study is open-label, pharmacodynamic assessment data should not be distritubed to sites until the patient has completed Month 6

The primary change occurs in Section 3.6, Blinding

Now reads: ~~Not applicable.~~ **While this is an open-label study, pharmacodynamic assessment data will not be distributed to the sites until after the patient has completed the Month 6 visit. Site personnel should refrain from obtaining or viewing local oxalate or glycolate assessments, except as medically indicated.**

Sections also containing this change:

- Section 6.3, Pharmacodynamic and Renal Assessments

Description: Clarify that additional liver function tests are performed when no alternative cause is identified.

The change occurs in Section 5.2.3.1, LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing item #3

Now reads: For any ALT or AST elevation >3× ULN:

a. If local laboratory results are obtained, confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.

~~c.~~ **b.** If an alternative cause is found, provide appropriate care.

~~b.~~ **c. If an alternative cause is not found,** perform assessments per Table 8 and Table 11.

Description: Clarify that specific study assessments may be conducted at a location other than the study center by a home healthcare professional.

The primary change occurs in Section 6, Study Assessments

Now reads: The schedules of study assessments is provided in Table 1, Table 2, Table 3, and Table 4**.** Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, abbreviated physical exam, and preparation and administration of study drug (at the discretion of the Investigator).

Sections also containing this change:

- Table 2 and Table 3, Schedule of Assessments: a footnote was added to highlight the study visits where study drug dosing may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability).

Description: Clarify that laboratory tests may be performed locally in certain cases.

The primary change occurs in Section 6.5.5, Clinical Laboratory Assessments

First paragraph now reads: The following clinical laboratory tests will be evaluated by a central laboratory**, except in cases where it is not feasible to perform all tests centrally due to blood draw volume limits, ie, in infants and very young patients, hematology, coagulation, and biochemistry panels may be performed locally, with central laboratory confirmation of any abnormalities.** Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal

range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 10 and will be assessed as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4).

Sections also containing this change:

- Table 11, Hepatic Assessments in Patients Who Experience Elevated Transaminases, footnote

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Description: Added study drug dosing instructions for patients whose disease progresses to requiring a dialysis regimen during the study

The primary change occurs in Section 5.2.2, Dose and Administration

The last paragraph now reads:

Patients whose disease progresses to requiring a dialysis regimen will continue on their planned dosing regimen prior to starting dialysis therapy. The lumasiran dose will be administered as soon as feasible following the end of dialysis, eg, within 2 hours of completing the dialysis session. If a patient does not receive a dose of lumasiran within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

Additional details can be found in the Pharmacy Manual.

Description: Updated the analysis population definitions.

The primary change occurs in Section 7.2.1, Populations to be Analyzed

Now reads:

The populations (analysis sets) are defined as follows:

- Safety Analysis Set: All patients who received any amount of study drug will be grouped according to the treatment actually received.
- **Efficacy Analysis Set: All patients who received any amount of lumasiran and have at least one valid spot urinary o:c ratio value at baseline and at least one valid spot urinary o:c ratio value from assessment(s) at Month 3 to Month 6.**
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data.

The **Safety Analysis Set will be used for safety analyses and sensitivity analysis of efficacy. The Efficacy Analysis Set will be used to evaluate efficacy endpoints.** ~~primary population used to evaluate efficacy, PD, and safety will be the Safety Analysis Set.~~ The PK Analysis Sets will be used to conduct PK analyses.

Sections also containing this change:

- Protocol synopsis
- Section 7.2.5, Efficacy Analyses
- Section 7.2.6, Pharmacodynamic Analysis

Description: Included description of the efficacy analysis methods

The primary change occurs in Section 7.2.5, Efficacy Analysis

First paragraph now reads:

The analysis of the efficacy endpoints will be based upon the ~~Safety~~ **Efficacy** Analysis Population. Descriptive summaries will be provided for the primary endpoint percent change in urinary oxalate excretion from baseline to Month 6. **The analysis will be performed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in spot urine oxalate:creatinine ratio. The model includes baseline value as covariate and fixed effect terms including treatment arm and visit (Months 3, 4, 5, 6). The treatment estimates from this model will represent an average percent change from baseline of spot urine oxalate:creatinine ratio across Month 3 through Month 6 at which the treatment effect is expected to have reached steady state. Furthermore, given the variability of spot oxalate:creatinine ratio, averaging the values across these visits will yield stable treatment estimates. Sensitivity analyses will be conducted to assess the robustness of the estimates and will be detailed in the SAP.** In addition, descriptive statistics ~~at each~~ scheduled visit will ~~also~~ be presented and by-patient listings and figures will be generated displaying all assessments (scheduled and unscheduled).

Description: Removed text instructing to see sample priority list in the Study Reference Manual; this text was added in error

The primary change occurs in Table 8, Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Table footnote now reads:

Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate. ~~See the Study Manual for sample priority list.~~

Description: Updated the protocol date and title of the Sponsor's approver

These changes are not listed individually.

Description: Correct typographical errors, punctuation, grammar, abbreviations, and formatting.

These changes are not listed individually.

ALN-GO1-004 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 04 MAY 2020

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

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter, dated 31 March 2020, to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. These changes are in line with guidance from both the European Medicines Agency and the United States Food and Drug Administration on the conduct of clinical trials during the COVID-19 pandemic.[EMA 2020; FDA 2020] The USMs are summarized in Section 1.1.

This protocol amendment also incorporates 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 patient safety and reduce patient burden regarding blood sampling. These changes are summarized in Section 1.2 and will not be implemented until appropriate Health Authority and Ethics Committee (EC) and/or Institutional Review Board (IRB) approval.

1.1. Urgent Safety Measures due to the Impact of the COVID-19 Pandemic

The USM modifications and new procedures are outlined below, and a detailed summary of the USMs is provided in Table 1. These changes were to be adopted immediately by the Investigator site per the Dear Investigator Letter.

- **Lumasiran dosing outside the study center by caregiver**

  Following appropriate training on lumasiran administration, dosing will be permitted at a location other than the study center (eg, at home) by the caregiver at all time points under the oversight of the Investigator and following consultation with the medical monitor. In addition, references to patient/caregiver instructions for administration and storage of study drug are now included within the protocol. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes for dosing.

  In order to assure uniform and comprehensive training and to assure compliance with the dosing instructions, the sponsor has prepared both Investigator and caregiver-facing written materials. The caregiver materials will provide detailed guidance on the scope of the self-administration allowance and detailed instructions on procedures surrounding dosing. These materials serve as a supplement to virtual training that caregivers will receive. The site-facing materials outline the investigator responsibilities under the self-administration scheme and provide a guide to the expectations around caregiver training.

In addition, investigators will make verbal contact with caregivers to assure compliance with protocol procedures and to assure that any adverse events or deviations are properly captured.

- **Time period to obtain weight for dose determination**

If the current procedure (weight obtained within 7 days prior to dose) is not possible due to the COVID-19 pandemic impacting activities at the study site or patient ability to access the site, the weight from up to 6 weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be used to calculate the amount of lumasiran to be administered.

Currently, the lightest patient in ALN-GO1-004 is 8.5 kilograms (kg), and the remaining patients are above 10 kg. Due to the considerable deceleration in the growth curve after infancy, dosing based on weight obtained during prior visit or 6 weeks for those on monthly dosing and 4 months for those on quarterly dosing would result in minimal under-dosing of approximately 5% relative to dosing obtained within 7 days prior to dose. In addition, since all patients have received multiple doses and the expected liver accumulation of lumasiran at steady state, potential under-dosing by about 5% is not expected to meaningfully influence the efficacy of lumasiran. On the other hand, the flexibility of using weight from prior visit is expected to reduce the potential for missed doses, which will in turn result in persistent suppression of liver oxalate production and continued suppression of urinary oxalate levels.

- **Assessment of adverse events, concomitant medications, renal stone events, and healthcare utilization**

In situations where a study visit is unable to be completed at the site or offsite by a healthcare professional visit, the study physician (or delegate) will verbally contact the patient to assess any adverse events, concomitant medications, renal stone events, and healthcare utilization within the study visit window.

- **Liver function tests**

Liver function test (LFT) results are to be obtained within 7◦days prior to dosing and results are to be reviewed prior to each dose of lumasiran. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes, when LFT assessments are not feasible within 7 days prior to the dose, LFT test results up to 6◦weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be reviewed to determine whether the dose can be administered. LFTs from the Week 2 visit must be reviewed prior to administration of the Month 1 dose.

This change in the window for LFT assessment is supported by data from our clinical trials. In the 75 patients with PH1 treated with lumasiran for a duration of up to 22 months, no clinically significant changes in LFTs due to lumasiran have been observed. Based on available data, lumasiran has an acceptable hepatic safety profile.

- **Study visits windows**

Except for assessments with other specified timing requirements, study assessments and dosing are to be performed within the following visit windows:

Screening through Month 6 (Protocol Table 1): Visit windows expanded from ±4 or ±7 in protocol amendment 1 to ±14 days; visits at least 14 days apart

After Month 7 for patients on monthly dosing (Protocol Table 2): Visit windows expanded from ±7 to ±14 days; visits at least 21 days apart

After Month 9 for patients on quarterly dosing (Protocol Table 4): Visit windows expanded from ±14 to ±28 days

- **Pharmacokinetic assessments**

Blood samples for PK assessment should continue to be collected at 2 and 4 hours postdose.

Blood samples for PK assessment may be collected at 8, 12, and 24 hours postdose as feasible during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes.

- **Vineland Adaptive Behavior Scale, and the Patient/Caregiver Experience and Impact Questionnaire**

Vineland Adaptive Behavior Scale, and the Patient/Caregiver Experience and Impact Questionnaire can be completed up to 4 months after the intended timepoint.

- **ECG and renal ultrasound assessments**

ECG and renal ultrasound assessments may be completed up to 3 months after the intended timepoint for assessments scheduled prior to Month 12, and up to 9 months after the intended timepoint for visits at Month 12 and later. This expansion of the ECG assessment window is supported by results of a clinical QTc assessment and nonclinical cardiac safety assessment of lumasiran, which demonstrated that lumasiran does not have QTc prolongation properties.

- **Assessments required to be performed in clinic**

Abbreviated physical examination/body system assessment, safety laboratory collection (blood and urine), PK and PD blood collection, and blood collection for vitamin B6 levels, ADA and exploratory analyses (blood and urine) assessments may be conducted offsite by a healthcare professional at all time points, where applicable country and local regulations and infrastructure allow.

- **Full physical examination**

If a visit is conducted offsite (eg, home), a body system assessment can be performed in lieu of a physical examination.

- **Impact of COVID-19**

Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient. Additional information regarding collection of this information, including completion of a new CRF specific to COVID-19, will be provided separately.

This change is implemented to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to study administration text**

Text was updated to provide clarification of Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

1.2. Changes Not Related to Urgent Safety Measures

The removal of the requirement to perform coagulation studies after screening reduces patient burden regarding the frequency of blood samples and the volume of blood collected, while ensuring patient safety. No safety signal pertaining to coagulation has been identified to date in any clinical study conducted with lumasiran. This modification is particularly important for pediatric patients given the greater limits placed on blood collection volumes. Additional changes to study conduct (outlined below) will not be implemented until appropriate HA and EC/IRB approval.

- Remove the measurement of coagulation from routine chemistry surveillance laboratory assessments
- Remove the requirement (after Month 12) for measurement of routine blood sample collection for pyridoxine (Vitamin B6) use as this was required to be stable up to Month 6 only. After Month 6, changes to standard of care therapies are permitted and this will be captured in concomitant medications.
- For patients on quarterly dosing (Table 4) during the long-term extension period, revised expectation to visit the site every 3 months to every 6 months after Month 24. Required assessments will be limited to weight, LFT laboratory assessments, single void urinary oxalate:creatinine, study dosing, and pregnancy testing if applicable, along with ongoing AEs, concomitant medications, and renal stone events information.

A detailed summary of these changes is provided in Table 2. Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting (including administrative changes between protocol amendments 1 and 2) are not detailed.

2. PROTOCOL AMENDMENT 2 DETAILED SUMMARY OF CHANGES

The primary section(s) of the protocol affected by the changes in Protocol Amendment 2 are indicated. The corresponding text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Table 1: Urgent Safety Measures COVID-19-related Changes to be Adopted Immediately

Purpose: To expand study visit windows.

The primary change occurs in Section 5.2.2, Dose and Administration

Revised text: **For patients who weigh <20 kg**, the dose will be based on a weight obtained within 7 days prior to dosing. **During periods of time when the COVID-19 pandemic impedes the ability of these patients to travel to the study site or healthcare professionals to go to patients' homes, a weight from up to 6 weeks prior to the planned monthly dose or up to 4 months prior to the planned quarterly dose may be used to calculate the amount of lumasiran to be administered.**

For patients who weigh ≥20 kg, the dose may be based on a weight obtained up to 4 months prior to the planned quarterly dose.

Section(s) also reflecting this change:

- Synopsis
- Column headings of the Schedules of Assessments (Table 1 through Table 4)
- Section 6.3.4, Renal Ultrasound
- Section 6.5.4, Electrocardiogram
- Section 6.7, Developmental Assessments
- Section 6.8, Patient/Caregiver Experience and Impact Questionnaire

Purpose: Expand the use of offsite administration to include lumasiran dosing by the caregiver and provide additional instructions on self administration, and preparation, handling, and storage of the study drug.

The primary change occurs in Section 5.2.2 Dose and Administration

Revised text: Study drug injections will be administered under the supervision of the Investigator. The site of injection may be the abdomen, the upper arms or thighs. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be **permitted** at a location other than the study center **(for example, the patient's home)** by a healthcare professional with the **oversight of the Investigator at all time points, provided the patient has tolerated at least 1 dose of lumasiran administered in the clinic.** However, continued study drug administration at the study center should be considered for patients who have ongoing study drug-related AEs, worsening injection site reactions with repeat dosing, or for anyone in the opinion of the Investigator who would benefit from clinical observation following dosing.

If the patient is unable to come to the study site, and a visit by a healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, lumasiran may be administered by the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the caregiver must receive appropriate training on lumasiran administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes for dosing.

Section(s) also reflecting this change:

- Bulleted notes beneath the Schedules of Assessments (Table 1 through Table 4)
- Section 3.1, Summary of Study Design
- Section 5.2.4. Preparation, Handling, and Storage
- Section 5.4. Treatment Compliance

Purpose: To reduce required collection timepoints prolonged clinic/home visits for PK assessments.

The primary change occurs in Table 5 (Pharmacokinetic Time Points: All Patients) and the bulleted notes beneath

Added text: **Blood samples for PK assessment may be collected at 8, 12, and 24 hours postdose as feasible during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes.**

Purpose: To extend the window for LFT assessment prior to dosing.

The primary change occurs in Section 5.2.3.1, Liver Function Test Criteria for Withholding, Monitoring and Stopping Lumasiran Dosing

Revised text: **For patients who weigh <20 kg,** ~~L~~liver function test (LFT) results (see Table 10) are to be obtained within 7 days prior to dosing and results are to be reviewed prior to each dose of lumasiran. **During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site or healthcare professionals to go to patients' homes and LFT assessments are not feasible within 7 days prior to the dose, LFT test results up to 6 weeks prior to the planned monthly**

dose or up to 4 months prior to the planned quarterly dose may be reviewed to determine whether the dose can be administered.

For patients who weigh ≥20 kg, LFT results may be reviewed up to 4 months prior to the planned quarterly dose to determine whether the dose can be administered.

Section(s) also reflecting this change:

- Section 5.2.2, Dose and Administration

Purpose: To allow continuous assessments (collected throughout the study) to be assessed via remote contact.

The primary change occurs in Table 1, Table 2, Table 3, and Table 4, Schedules of Assessment

Added text: • **In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, renal stone events, adverse events, and healthcare utilization.**

Purpose: Allow flexibility for scope of physical examination; pregnancy testing when offsite visits occur.

The primary change occurs in 1) Section 6.5.3, Physical Examination, and 2) Section 6.5.5.2, Pregnancy Testing

Added text: 1) Abbreviated physical examinations **(body system assessment)** will include examination of at least the following: respiratory, cardiovascular, dermatological, gastrointestinal, and musculoskeletal systems.

If a visit is conducted offsite (eg, at the patient's home), a body system assessment may be performed in lieu of a physical examination.

2) **Pregnancy testing may be performed offsite by a caregiver if a caregiver will be administering study drug.**

Purpose: Collect information related to the impact of the COVID-19 pandemic on patient participation in the study.

The primary change occurs in an added Section **6.5.7, COVID-19 Data Collection**

Added text: **Information on the COVID-19 infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.**

Section(s) also reflecting this change:

- Section 7.2 Statistical Methodology

Purpose: Revise and update informed consent instructions.

The primary change occurs in Section 8.1.1, Informed Consent

Added text: **The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.**

Purpose: Revise and update ethical review instructions.

The primary change occurs in Section 8.1.2, Ethical Review

Added text: In addition, the IRB or IEC must approve all advertising used to recruit patients for the study **(except those that support the need to remove an apparent immediate hazard to the patient)**.

Table 2: Changes Not Related to Urgent Safety Measures to be Implemented After Health Authority and Ethics Committee(EC)/Institutional Review Board (IRB) Approval, where applicable

Purpose: Removes the requirement (after Month 12) for measurement of routine blood sample collection for pyridoxine (Vitamin B6) use.

The primary change occurs in the Table 2, Schedule of Assessments – Long-term Extension Period (Month 7 to Month 35): Patient Weight <10 kg

Deleted text: X was deleted from schedule of assessment timepoints later than Month 12.

Table(s) also reflecting this change:

- Removed entirely from Schedules of Assessments for the Long-term Extension Period (Table 3 and Table 4)
- Table 10, Clinical Laboratory Assessments (footnote)

Purpose: To reduce the number of assessments conducted in the clinic after Month 24.

The primary change occurs in Table 4, Schedule of Assessments Long-term Extension Period (Month 9 to End of Study): Patient Weight ≥10 kg

Revised text: Removed Xs from Table 4 in order to: remove the abbreviated physical exam; revise routine safety laboratory assessments from every 3 months to once every 6 months (with the exception of LFTs); adjust blood samples collected for PD analyses to be optional every 3 months; reduce the number of single-void urine collections, and move exploratory blood and urine collections to the once every 6 months clinic visit.

Purpose: Removes the requirement for measurement of routine coagulation clinical laboratory assessments.

The primary change occurs in Section 6.5.5, Clinical Laboratory Assessments Table 10

Revised text:

~~**Coagulation**~~	
~~Prothrombin time~~	~~International Normalized Ratio~~
~~Partial Thromboplastin Time~~	

Section(s) also reflecting this change:

- Section 5.2.3, Dose Modifications; Table 8: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified
- Section 6.5.5.3, Additional Liver Function Assessments

3. REFERENCES

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards (03/2020; updated 16/04/2020). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, (20/03/2020; updated 27/03/2020; updated 28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf