Official Title:	**ILLUMINATE-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients With Advanced Primary Hyperoxaluria Type 1 (PH1)**
NCT Number:	**NCT04152200**
Document Date:	**Clinical Study Protocol, 06 May 2020**

CLINICAL STUDY PROTOCOL
ALN-GO1-005

Protocol Title:	ILLUMINATE-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1)
Short Title:	A Study to Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C)
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2019-001346-17
IND Number:	128941
Protocol Date:	Original protocol, 16 May 2019 Amendment 1, 06 May 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PI [redacted]

SPONSOR PROTOCOL APPROVAL

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

PI

[redacted]

Alnylam Pharmaceuticals, Inc.

7 May 2020

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-005 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-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1)

Short Title

A Study to Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C)

Study Drug

Lumasiran (ALN-GO1)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 15 clinical study centers across 10 countries.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Cohort A • Evaluate the effect of lumasiran on plasma oxalate in patients who are not on dialysis therapy **Cohort B** • Evaluate the effect of lumasiran on plasma oxalate levels in patients who are on dialysis therapy	**Cohort A** • Percent change in plasma oxalate from Baseline to Month 6 **Cohort B** • Percent change in pre-dialysis plasma oxalate from Baseline to Month 6
Secondary	
• Evaluate the effect of lumasiran on change in plasma oxalate area under the curve (AUC) between dialysis sessions • Evaluate the long-term effects of lumasiran on change in plasma oxalate • Evaluate the effect of lumasiran on change in urinary oxalate excretion • Evaluate quality of life in patients with PH1 • Characterize the PK of lumasiran • Evaluate the effect of lumasiran on nephrocalcinosis • Evaluate the effect of lumasiran on dialysis requirements	<u>Primary Analysis Period (Baseline to 6 months)</u> • Percent change in plasma oxalate AUC between dialysis sessions • Absolute change in plasma oxalate • Change in the following parameters: o Urinary oxalate

Objectives	Endpoints
• Evaluate the effect of lumasiran on the occurrence of renal stones • Evaluate the effect of lumasiran on renal function • Evaluate the effect of lumasiran on change in measures of systemic oxalosis	○ QoL assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent • Plasma PK parameters of lumasiran <u>Long-term Extension Period (6 months to end of study)</u> • Percent change in plasma oxalate AUC between dialysis sessions • Percent and absolute change in plasma oxalate • Change in the following parameters: ○ Nephrocalcinosis as assessed by renal ultrasound ○ Frequency and mode of dialysis ○ Frequency of renal stone events ○ Urinary oxalate ○ Renal function as assessed by eGFR ○ Measures of systemic oxalosis in the following systems: ▪ Cardiac ▪ Dermatologic ▪ Skeletal ▪ Ocular ○ QoL(Quality of life) assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent
Exploratory	
• Evaluate growth parameters and developmental milestones in patients who are <6 years of age at consent • Evaluate quality of life in patients with PH1 • Evaluate the effects of lumasiran on patient and caregiver resource use	• Growth parameters in patients who are <6 years of age at consent • Change in developmental milestones over time in patients <6 years of age at consent • Change in QoL as assessed by EQ-5D-Y and PedsQL (individual subscales of the generic and ESRD modules, and ESRD module total

Objectives	Endpoints
• Describe patient experiences on lumasiran in PH1 patients and the experiences of caregivers for these patients • Assess for antidrug antibodies (ADA) against lumasiran • Evaluate the effects of lumasiran on additional pharmacodynamic (PD) parameters of plasma glycolate and urinary glycolate	score) for patients ≥2 to 18 years of age at consent, and as assessed by EQ-5D-5L in patients ≥18 years of age at consent • Change in QoL as assessed by KDQOL Symptoms and Problems of Kidney Disease subscale in patients ≥18 years of age at consent • Change in patient and caregiver resource use (eg, work/school attendance, visits to doctor/hospital) • Change in patient and caregiver experiences as evaluated by a patient experience questionnaire and a caregiver experience questionnaire • Frequency of ADA • Change in urinary and plasma glycolate
Safety	
• Evaluate the safety and tolerability of lumasiran	• Frequency of adverse events

Study Design

This is a multicenter, single arm study designed to evaluate the efficacy, safety, PK and PD of lumasiran in patients with a documented diagnosis of PH1 who have advanced renal disease, as evident by eGFR ≤45 ml/min/1.73 m^2 (or serum creatinine elevated for age, in patients <12 months of age). All eligible patients will be administered open-label lumasiran; no control group will be assessed. This study will consist of 2 periods: a 6-month primary analysis period followed by a long-term (54 months) extension period.

This study will include 2 cohorts: Cohort A and Cohort B. Cohort A will include patients who do not yet require dialysis. Cohort B will include patients who are on dialysis therapy. Dialysis modality will be restricted to patients on hemodialysis only. Enrollment to both cohorts will occur concurrently. Cohort A patients who experience progression of renal impairment over time and begin to require dialysis therapy will cross-over to Cohort B. During the first 6 months of the study, patients who cross-over may be replaced in Cohort A.

Patients will be screened from Day -120 to Day -1 to determine eligibility. Consented patients meeting all eligibility criteria will receive their first dose of lumasiran on Day 1. Lumasiran will be administered subcutaneously (SC) utilizing weight-based dosing.

As specified in the Schedules of Assessments, blood samples will be collected in both cohorts for plasma oxalate sample analysis, to establish plasma oxalate profiles (AUC) in Cohort B, and for PK parameter analysis in both cohorts. In Cohort B, dialysis status and changes in dialysis regimen will also be monitored. During the first 6 months of the study, changes to dialysis regimen will not be permitted, except when medically necessary.

Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, electrocardiograms (ECGs), physical examinations, and concomitant medications.

Number of Planned Patients

The planned enrollment for this study is 20 patients, including 6 patients in each cohort. Of those 20 patients, the planned enrollment includes 4 patients who are <6 years of age at consent, and 2 patients between ≥6 to <18 years of age at consent.

Diagnosis and Main Eligibility Criteria

This study will include full term infants to adults with a documented diagnosis of PH1 confirmed by genetic analysis, eGFR ≤45 mL/min/1.73 m^2 at screening in patients ≥12 months of age (in patients <12 months of age, must have serum creatinine considered elevated for age), plasma oxalate ≥20 µmol/L at screening, if on pyridoxine therapy must be stable regimen for at least 90 days prior to informed consent and remain on regimen through Month 6 visit, and must be willing and able to comply with all study requirements and provide informed consent (and assent, as applicable) per local and national requirements. Patients on dialysis may be on hemodialysis therapy only and must have been on a stable regimen for at least 4 weeks; patients who are on hemodialysis/peritoneal dialysis combination therapy or peritoneal dialysis alone will be excluded from the study.

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, blocking production of glycolate oxidase (GO) and hence reducing hepatic oxalate production. Lumasiran will be supplied as a sterile solution in water for SC injection. A weight-based dose regimen will be employed 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

Reference Treatment, Dose, and Mode of Administration

Not applicable.

Duration of Treatment and Study Participation

The duration of treatment with lumasiran is up to 60 months, with final dose administered at the Month 57 visit. The estimated total time on study for each patient is up to 64 months, including up to 4 months of screening.

Statistical Methods

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

The Safety Analysis Set will include all patients who received any amount of lumasiran during the study. The Efficacy Analysis Set will include all patients who received any amount of lumasiran and have at least 1 valid plasma oxalate value at Baseline and at the Month 3 assessment or beyond. The PK Analysis Set will include all patients who received any amount

of lumasiran have at least 1 postdose blood sample for PK parameters and have evaluable PK data.

The primary population used to evaluate efficacy will be the Efficacy Analysis Set and safety will be the Safety Analysis Set. The PK Analysis Sets will be used to conduct PK analyses.

The primary analysis is percent change from baseline in plasma oxalate (Cohort A) / pre-dialysis plasma oxalate (Cohort B) summarized through Month 6 by cohorts. Secondary endpoints will be analyzed and reported with by-patient listings and by-patient figures of actual values, change from baseline and percent change (where change in percent is applicable) at each visit (scheduled and unscheduled visits). Tabular summaries using descriptive statistics (mean, standard error, median, min, max) will be reported. Long-term treatment effect of lumasiran will be summarized descriptively for the long-term extension period. Safety data will be summarized descriptively and presented in by-patient listings.

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**							
			D1	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)*	**Notes**	**-120 to -1**	**1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**
Informed consent	Section 8.1.1	X								
Demographics	Section 6.1	X								
Medical history	Section 6.1	X	X							
Inclusion/exclusion criteria	Section 4.	X								
Full PE	Section 6.5.3	X								X
Abbreviated PE	Section 6.5.3		X	X	X	X	X	X	X	
Height/length	Section 6.5.2	X	X		X (<6 y)	X (<6 y)	X	X (<6 y)	X (<6 y)	X
Body weight	Section 6.5.2	X	X		X	X	X	X	X	X
Vital signs	Section 6.5.1	X	X	X	X	X	X	X	X	X
12-lead ECG	Triplicate. Repeat if done ≥60 days before D1. Section 6.5.4	X					X			X
Follicle-stimulating hormone	Section 6.5.5.2	X								
Pregnancy test	Females of child-bearing potential. Section 6.5.5.2	X	X		X	X	X			X
DNA sample for PH1/*AGXT* mutation analysis	Section 6.1	X								
Exploratory DNA sample	Optional. Section 6.6	X								
Clinical laboratory assessments	Repeat serum creatinine and LFTs if collected ≥30 days before D1; Section 6.1. Section 6.5.5	X	X	X	X	X	X	X	X	X
Coagulation (PT/PTT/INR)		X								
Study drug dosing in pts <10 kg	Table 10. Dose after dialysis, if applicable.-Doses must be at least 21 days apart. Section 5.2.2		X		X	X	X	X	X	X
Study drug dosing in pts ≥10 kg			X		X	X	X			X
Blood samples for PK analyses	Table 5 and Table 6		X							X
Urine samples for PK analyses	Table 7		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		**Screening**	**6-Month Primary Analysis Period**							
Study Visit			**D1**	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)*	**Notes**	**-120 to -1**	**1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**
Blood samples for PD analyses (Cohort A)	Screening collections as per Figure 1, Section 6.3	X			X	X	X	X	X	X
Blood samples for PD analyses (Cohort B)	Screening collections as per Figure 1, Section 6.3	X			X	X	X	X	X	X
Blood samples for POx profile	Table 6; Pts on dialysis only. Screening collections as per Section 6.1 Figure 1.	X					X			X
24-hour urine collection (1 collection)	Table 12 and Section 6.2.2						X			
24-hour urine collection (3 collections)		X								X
Single-void urine collections (3 collections).	Collected within 7 days predose (first morning voids preferred). Section 6.2.2	X			X	X	X	X	X	X
Blood sample for pyridoxine (vitamin B6) levels	Only in pts receiving therapeutic pyridoxine, collect ≥6 hrs after dose. Section 5.3	X	X				X			X
Renal ultrasound	Section 6.3.1	X								X
Echocardiogram	Repeat if done ≥60 days before D1. Section 6.2.3.1	X								X
Radiographs	Section 6.2.3.3	X								
Ophthalmology Evaluation	Section 6.2.3.4	X								
Review/Record Dialysis Parameters	Pts on dialysis. Section 6.5.5.5	X	X				X			X
Vineland Behavior Scale	Pts <6 y at consent. Section 6.7	X								X
Quality of life questionnaires	Section 6.8	X								X
Patient/caregiver experience and impact questionnaires	Section 6.9	X								X
Healthcare resource utilization	Section 6.10	Continuous								
ADA sample	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**							
			D1	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Study Day (±Visit Window)*	**Notes**	**-120 to -1**	**1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**
Blood and urine samples for exploratory analyses	Single-void urine. Samples collected predose. Section 6.6	X	X		X		X			X
Bone scan (Optional)	Only in adult Cohort B pts Section 6.2.3	X								
Renal stone events	Section 6.3.2	Continuous								
Review/record AEs	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; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; hrs=hours; LFTs=liver function tests; M=Month; Opt=optional; PD=pharmacodynamic; PE=physical examination; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; POx=plasma oxalate; pts=patients; SAE=serious adverse event; wk=week; y=year(s)
* During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, the visit window is expanded to ±14 days after Week 2.
Notes:

- One month is defined as 28 days.
- Only SAEs are collected in the Screening period. Starting on D1, all AEs (including SAEs) are collected.
- 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 (Section 3.3.1). See Section 4.3.1 for instructions for patients who discontinue study drug.
- Urine collections are only performed in patients who are able to produce urine, ie, ability to produce ≥100 ml per day.

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 Period		**Long-term Extension Period**																	
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 (±7)**	**253 (±7)**	**281, 309 (±7)**	**337 (±7)**	**365, 393 (±7)**	**421 (±7)**	**449, 477 (±7)**	**505 (±7)**	**533, 561 (±7)**	**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 PE	Section 6.5.3				X				X				X				X			
Abbreviated PE	Section 6.5.3	X	X	X		X	X				X				X				X	
Height/length	Section 6.5.2	X	X	X	X	X	X		X		X		X		X		X		X	
Body weight	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	Triplicate. Section 6.5.4				X								X							
Clinical laboratory assessments	LFTs within 7 days predose. 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	LFT only
Study drug dosing	Table 10. Dose after dialysis, if applicable. Doses must be ≥21 days apart. Section 5.2.2	X	X	X	X	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	
Blood samples for POx profile	Pts on dialysis only. Table 6				X															
24-hour urine collection (1 collection)	Table 12 and Section 6.2.2				X				X				X				X			
Single-void urine collections (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2.2		X		X		X		X		X		X		X		X		X	
Blood sample for pyridoxine (vitamin B6) levels	Only in pts receiving therapeutic pyridoxine, collect ≥6 hrs after dose. Section 5.3		X		X															
Renal ultrasound	Section 6.3.1				X								X							
Echocardiogram	Section 6.2.3.1				X								X							
Radiographs	Section 6.2.3.3				X								X							
Ophthalmology Evaluation	Section 6.2.3.4				X								X							
Review/Record Dialysis Parameters	Pts on dialysis only. Section 6.5.5.5		X		X		X		X		X		X		X		X		X	
Vineland Behavior Scale	Pts <6 y at consent. Section 6.7				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 Period		**Long-term Extension Period**																	
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 (±7)**	**253 (±7)**	**281, 309 (±7)**	**337 (±7)**	**365, 393 (±7)**	**421 (±7)**	**449, 477 (±7)**	**505 (±7)**	**533, 561 (±7)**	**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)**
Quality of life questionnaires	Section 6.8				X				X				X				X			
Patient/caregiver experience and impact questionnaires	Section 6.9				X				X				X				X			
Healthcare resource utilization	Section 6.10	Continuous																		
ADA sample	Section 6.5.5.1				X				X				X				X			
Blood and urine samples for exploratory analyses	Single-void urine. Samples collected predose. Section 6.6		X				X				X				X				X	
Renal stone events	Section 6.3.2	Continuous																		
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; LFT=liver function tests; M=month; Opt=optional; PD=pharmacodynamic; PE=physical examination; PK=pharmacokinetic; POx=plasma oxalate; pts=patients; SAE=serious adverse event

* During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, study assessments and dosing may be performed within ±14 days of the visit unless otherwise noted.

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 (Section 3.3.1). See Section 4.3.1 for instructions for patients who discontinue study drug.
- Urine collections are only performed in patients who are able to produce urine, ie, ability to produce ≥100 ml per day.

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)**
Full PE	Section 6.5.3	X				X				X				X			X	
Abbreviated PE	Section 6.5.3			X				X				X				X		X
Height/length	Section 6.5.2	X		X		X		X		X		X		X		X	X	X
Body weight	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	Triplicate. Section 6.5.4	X								X							X	
Clinical laboratory assessments	LFTs within 7 days predose. 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	Table 10. Dose after dialysis, if applicable. Doses 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		
Blood samples for PD analyses	Section 6.3	X		X		X		X		X		X		X		X	X	X
Blood samples for POx profile	Pts on dialysis only. M36, M48 only if systemic oxalosis manifestation Table 6	X								X								
24-hour urine collection (1 collection)	Table 12 and Section 6.2.2	X				X				X				X			X	
Single-void urine (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2.2	X								X							X	X
Single-void urine (1 collection)				X		X		X				X		X		X		
Renal ultrasound	Section 6.3.1	X								X							X	
Echocardiogram	Section 6.2.3.1	X								X							X	
Radiographs	Section 6.2.3.3	X								X							X	
Ophthalmology Evaluation	Section 6.2.3.4	X								X							X	
Review/record dialysis parameters	Pts on dialysis only. Section 6.5.5.5	X		X		X		X		X		X		X		X	X	
Vineland Behavior Scale	Pts <6 y at consent. Section 6.7	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)**
Quality of life questionnaires	Section 6.8	X				X				X				X			X	
Patient/caregiver experience and impact questionnaires	Section 6.9	X				X				X				X			X	
Healthcare resource utilization	Section 6.10	Continuous																
ADA sample	Section 6.5.5.1	X				X				X				X			X	X
Blood and urine samples for exploratory analyses	Single-void urine. Samples collected predose. Section 6.6			X				X				X				X	X	
Renal stone events	Section 6.3.2	Continuous																
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; LFT=liver function tests; M=month; PD=pharmacodynamic; PE=physical examination; PK=pharmacokinetic; POx=plasma oxalate; pts=patients; SAE=serious adverse event; y=years

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 (Section 3.3.1). See Section 4.3.1 for instructions for patients who discontinue study drug.
- Urine collections are only performed in patients who are able to produce urine, ie, ability to produce ≥100 ml per day.

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 (±14)**	**337 (±14)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**841 (±14)**	**925 (±14)**	**1009 (±14)**	**1093 (±14)**	**1177 (±14)**	**1261 (±14)**	**1345 (±14)**	**1429 (±14)**	**1513 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Full PE	Section 6.5.3		X		X		X				X				X				X	
Abbreviated PE	Section 6.5.3	X		X					X				X				X			X
Height/length	Section 6.5.2		X		X		X		X		X		X		X		X		X	X
Body weight	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	Triplicate. Section 6.5.4		X				X				X				X				X	
Pregnancy test	Females of child-bearing potential. Section 6.5.5.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory assessments	LFTs within 7 days predose. Section 6.5.5	X	X	X	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	LFT only	X	X
Study drug dosing	Table 10. Dose after dialysis, if applicable. Section 5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for PD analyses	M12, M36, M48, only if POx profile is not performed. Section 6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for POx profile	Pts on dialysis only. M36, M48 only if systemic oxalosis manifestation. Table 6		X								X				X					
24-hour urine collection (1 collection)	Table 12 and Section 6.2.2		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 (±14)**	**337 (±14)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**841 (±14)**	**925 (±14)**	**1009 (±14)**	**1093 (±14)**	**1177 (±14)**	**1261 (±14)**	**1345 (±14)**	**1429 (±14)**	**1513 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Single-void urine collections (3 collections)	Collected within 7 days predose (first morning voids preferred). Section 6.2.2	X	X	X	X		X		X		X				X				X	X
Single-void urine collection (1 collection)						X		X		X		X		X		X		X		
Blood sample for pyridoxine (vitamin B6) levels	Only in pts receiving therapeutic pyridoxine, collect ≥6 hrs after dose. Section 5.3	X	X																	
Renal ultrasound	Section 6.3.1		X				X				X				X				X	
Echocardiogram	Section 6.2.3.1		X				X				X				X				X	
Radiographs	Section 6.2.3.3		X				X				X				X				X	
Ophthalmology Evaluation	Section 6.2.3.4		X				X				X				X				X	
Review/record dialysis parameters	Pts on dialysis only. Section 6.5.5.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vineland Behavior Scale	Pts <6 y at consent. Section 6.7		X		X		X		X		X		X		X		X		X	
Quality of life questionnaires	Section 6.8		X		X		X		X		X		X		X		X		X	
Patient/ caregiver experience and impact questionnaires	Section 6.9		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 (±14)**	**337 (±14)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**841 (±14)**	**925 (±14)**	**1009 (±14)**	**1093 (±14)**	**1177 (±14)**	**1261 (±14)**	**1345 (±14)**	**1429 (±14)**	**1513 (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Healthcare resource utilization	Section 6.10	Continuous																		
ADA sample	Section 6.5.5.1		X		X		X		X		X		X		X		X		X	X
Blood and urine samples for exploratory analyses	Single-void urine. Samples collected predose. Section 6.6	X		X		X		X		X		X		X		X		X	X	
Bone scan (Optional)	Only in adult Cohort B pts. Section 6.2.3		X								X								X	
Renal stone events	Section 6.3.2	Continuous																		
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; LFT=liver function tests; M=month; PD=pharmacodynamic; PE=physical examination; PK=pharmacokinetic; POx=plasma oxalate; pts=patients; SAE=serious adverse event; y=years

* During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, study assessments and dosing may be performed within ±28 days of the visit unless otherwise noted.

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 (Section 3.3.1). See Section 4.3.1 for instructions for patients who discontinue study drug.
- Urine collections are only performed in patients who are able to produce urine, ie, ability to produce ≥100 ml per day.

Table 5: Pharmacokinetic Assessment Time Points for Patients Not on Dialysis

Study Visit	Protocol Time (hh:mm)
Day 1	02:00 (±20 minutes)
	04:00 (±30 minutes)
	08:00 (±1 hours)
	12:00 (±2 hours)
	24:00 (±3 hours)
Month 6 (±3 mos)	02:00 (±20 minutes)
	04:00 (±30 minutes)
	08:00 (±1 hours)
	12:00 (±2 hours)
	24:00 (±3 hours)

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

- Blood samples for PK assessment may be collected at 8 and 12 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 limit permits (see Section 6.5.5.4)
- See Section 6.4 for additional information on PK assessments.

Table 6: Pharmacokinetic and Plasma Oxalate Profile Assessment Time Points for Patients on Dialysis

Sampling Time (hh:mm)	**Blood sample for PK Assessment**		**Blood Sample for POx Profile Assessment**
Study Month (Study Day)	**Day 1**	**Month 6***	**Screening Period (Day -120 to Day -1) Month 3, Month 6, and Month 12****
Pre-dialysis			X
30 minutes before end of dialysis (±10 minutes)			X
00:30 (post-dialysis) (±30 minutes)			X
02:00 (postdose) (±20 minutes)	X	X	X
04:00 (postdose) (±30 minutes)	X	X	X
08:00 (postdose) (±1 hour)	X, *if feasible*	X	X
12:00 (postdose) (±2 hours)	X, *if feasible*	X	X
Pre-dialysis (for HD session day after dose) 24:00 post-dose (±3 hours) if no HD session scheduled the day after dosing	X	X	X

Abbreviations: HD=hemodialysis; hh:mm=hour:minute; hrs=hours; mos=months; PK=pharmacokinetics; POx=plasma oxalate

* During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, the blood sample for PK assessment may be collected at Month 6 (±3 months).

**During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, blood samples for the plasma oxalate assessment maybe collected at Month 3 (±2 months), Month 6 (±5 months), and Month 12 (±11 months), and may be obtained post dialysis at 2:00, 4:00, 8:00, 12:00, and 24:00 timepoints on non-dosing days.

- The 8- and 12-hour timepoints of the POx profile assessment will only be performed at selected study centers.
- When feasible, POx assessment should be performed after the shortest interval between dialysis sessions, ie, starting on or after the second dialysis session of the week. This applies to all patients on dialysis, regardless of the number of days in treatment regimen. The timing of POx assessments relative to dialysis should remain consistent throughout the study (ie, after the shortest interval between dialysis sessions if this was done during screening). During the first 6 months on study, the starting time for the predialysis POx levels (including those in POx profiles) is 24 hrs (±2 hrs) after a dialysis session on the previous day or 48 hrs (±4 hrs) after previous session in patients on 3 days per week dialysis regimen. See Section 6.1 for information regarding interruption of dialysis regimen during the screening period.
- After the first 6 months, the timing of the POx assessment relative to patients' dialysis schedule should continue to remain consistent for each patient, when possible.
- Suggested sample times are listed. The hour (±range) indicates sample collection timing relative to dosing and end of dialysis session. Precise sample times (hour and minute) are recorded.
- At Screening, the timepoints described above are relative to beginning and end of dialysis sessions. See Figure 1 for further details about timing of POx profile assessments.
- POx profile assessment will also be performed at Month 36 and Month 48 only in patients with at least one systemic oxalosis manifestation.
- See Section 6.4 for additional information on PK assessments.
- If an SAE occurs associated with dosing, an additional PK sample may be collected at 4 to 8 hrs postdose on the day of dosing, where blood volume permits (see Section 6.5.5.4).

Table 7: Urine Pharmacokinetic Assessment Time Points for Patients with Urine Production, in Patients >6 years old

Study Day	Sampling Time (postdose) (hh:mm)	Pooled Urine PK Sample
Day 1	0-6 hours (±30 minutes)	X
	6-12 hours (±30 minutes)	X
	12-24 hours (±2 hours)	X

Abbreviations: hh:mm=hour minute; PK=pharmacokinetics

- Suggested sample times are listed. The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded.
- Collected only in patients who are able to produce urine, ie, ability to produce ≥100 ml urine per day.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
AGT	Alanine-glyoxylate aminotransferase
AGXT	Alanine-glyoxylate aminotransferase gene
ALT	Alanine aminotransferase
ASGPR	Asialoglycoprotein receptor
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
24h	24 hours
HAO1	Hydroxyacid oxidase 1
HBV	Hepatitis B virus
HCV	Hepatitis C virus

Abbreviation	Definition
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
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
SUSAR	Suspected unexpected serious adverse reaction
$t_{½\beta}$	Elimination half-life
t_{max}	Time to maximum plasma concentration
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 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 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 2013] Without treatment, the disease progresses inexorably, and death from end-stage renal disease (ESRD) and/or complications of oxalosis is inevitable.[Cochat 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 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 1996]

PH1 often presents as a pediatric disease, and 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 of age, 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; disease presented in infancy in 29% of patients, 40% of whom had ESRD.[Mandrile 2014] Overall, 43% of all patients diagnosed with PH1 had already progressed to ESRD at the time of 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 in

those that do not yet have ESRD. Pyridoxine can normalize hepatic oxalate production (and consequently urinary oxalate) in a small subset (~5%) of patients.[Hoppe 2010] Dietary modification plays a minor role in treatment since endogenous oxalate production far exceeds dietary intake in patients with PH1. Patients progressing to, or presenting with ESRD, require intense dialysis replacement therapy. Dialysis is not viewed as an effective therapy for PH1, but rather serves as a step in the clinical course toward 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 typically 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 2013], and intense use of health care resources.

PH1, over time, develops into a serious, severely debilitating disease with significant morbidity and mortality which have a profoundly negative impact on quality of life. In renally impaired patients, plasma oxalate saturation and persistent deposition across multiple organs leads to systemic oxalosis manifestations. Given the clinical course and characteristics of PH1 disease progression, it is reasonable to expect that decreases in hepatic oxalate production may result in clinical benefit in PH1 patients with advanced renal disease. Limited and burdensome management options for PH1 outlined above highlight the serious unmet need for a safe and efficacious treatment for all patients with this devastating disease, regardless of renal function.

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 infants, pediatric, and adult patients.

A detailed description of the chemistry, pharmacology, efficacy, and safety of lumasiran is provided in 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.

Notably, an in vitro study using human hepatocyte showed that infants have similar ASGPR mRNA and protein levels as adults, indicating that siRNA uptake into the liver will not be influenced by age.

In addition, the PK and PD evaluations of lumasiran and two additional siRNAs in subtotal nephrectomy model in rats, where 5/6th of the kidneys was removed to mimic severe renal impairment, showed no meaningful differences in plasma or liver PK, and no differences in PD in rats with and without nephrectomy.

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 Investigator's Brochure.

1.2.2. Summary of Clinical Data with Lumasiran

Lumasiran is being investigated in 4 clinical studies, 3 of which are currently ongoing. Study ALN-GO1-001 is a Phase 1/2 study, and was completed 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. 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.

Available preliminary data from Study ALN-GO1-001 demonstrate a mean maximal reduction in 24-hour urinary oxalate of 64% (Cohorts 1 to 3) and achievement of normal to near-normal levels of urinary oxalate (<0.7 mmol/24h/1.73 m^2) in patients dosed with lumasiran (range: 0.29 to 0.67 mmol/24h/1.73 m^2). This suppression of urinary oxalate was maintained with repeat dosing, indicative of the durability of the pharmacodynamic effect of lumasiran. In addition, in the multiple-ascending dose group (Part B; n=10), preliminary data showed a mean reduction of 59% in plasma oxalate relative to baseline 28 days after the last dose. The mean maximal reduction in plasma oxalate was 75% (range 57-94%), and 50% of patients achieved plasma oxalate levels within the normal range (<1.6 μmol/L).

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

In the ALN-GO1-001 and ALN-GO1-002 clinical studies, available data 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.

Additional detailed information on the chemistry, pharmacology, efficacy, and safety of lumasiran is provided in the Investigator's Brochure.

1.3. Study Design Rationale

Elevated oxalate is the direct cause of disease pathology (kidney stones, renal failure, and systemic oxalosis) in patients with PH1, and can be evaluated as plasma oxalate level, plasma oxalate AUC between dialysis sessions, urinary excretion of oxalate, and measures of systemic oxalosis. As discussed in Section 1.2.2, meaningful reductions in urinary oxalate excretion were seen in the Phase 1/2 study, ALN-GO1-001. In addition to reducing urinary oxalate, lumasiran is expected to significantly lower plasma oxalate levels in patients with renal impairment based on the observed decrease in plasma oxalate levels in clinical studies of patients with preserved renal function. PH1 patients with advanced renal disease (eGFR $\leq$45 mL/min/1.73 m^2), who have severe unmet medical need, are also expected to meaningfully benefit from decreased hepatic oxalate production, regardless of whether or not on dialysis therapy. The majority of PH1 patients in the United States present in early childhood and many progress to renal failure by early adulthood. Up to 26% of PH1 patients present with severe infantile disease and can develop end stage renal disease (ESRD) as early as 4 to 6 months of age.[Harambat 2010; Hopp 2015] Therefore, it is justified to study the effect of lumasiran in a PH1 population with advanced renal disease, ranging from full term infants to adults.

The weight-based dosing regimen of this study, for PH1 patients with advanced renal disease, is similar to those being studied (studies ALN-GO1-003, ALN-GO1-004) in PH1 patients of the same age range as this study, with less advanced renal disease and is described in Section 5.2.2. Preclinical and clinical data indicate renal impairment does not influence the systemic exposure, PD, or safety of siRNA compounds (see Section 1.4).

This study will evaluate PH1 patients with advanced renal disease in separate cohorts to account for differences in patients who do not yet require dialysis (Cohort A) vs patients who are currently on a dialysis maintenance regimen (Cohort B). The objectives and endpoints reflect the differences in clinical management between cohorts during both the Primary Analysis Period (Baseline to 6 months) and the Long-term Extension Period (Month 6 to End of Study; 54 months total). The primary objective of plasma oxalate reduction applies to both cohorts. Also, the following can be measured regardless of dialysis dependence status and objectives are the same for both cohorts: evaluation of growth parameters and developmental milestones (in children <6 years of age), quality of life, caregiver resource use, patient/caregiver experiences on lumasiran, antidrug antibodies (ADA), and additional PD parameters of plasma and urinary glycolate. In addition, to further evaluate the effect of lumasiran on disease progression, measures of systemic oxalosis will be assessed across multiple organ systems, ie, cardiac, dermatologic, skeletal, and ocular.

Multiple samples will be collected for evaluation of plasma oxalate level (in both cohorts) and 2 separate plasma oxalate profile assessments (in Cohort B only, to calculate AUC between dialysis sessions) will be performed during Screening to establish robust baseline measurements of the primary and secondary endpoints. The primary endpoint is an objective laboratory assessment and not subject to bias. Due to the combination of patient heterogeneity of a population spanning full term infants to adults, heterogeneity of disease characteristics in the broad age range, and the ultra-rare orphan population, a single-arm design is employed for this study.

Lumasiran is currently being investigated in 4 separate clinical studies comprising infant, pediatric and adult populations of patients with PH1 who have relatively preserved renal function with regard to oxalate excretion by the kidneys. In this study, lumasiran will be evaluated in PH1 patients of all ages with advanced renal disease, including patients on dialysis. Enrolling infants and young pediatric patients in this study is acceptable given that lumasiran has been well tolerated in children ≥6 years old, and PH1 can present as a pediatric disease with life-threatening consequences as early as infancy, with particularly high unmet medical need in this subpopulation with impaired renal function.

1.4. Dose Rationale

Contribution of Renal Pathway on the Pharmacokinetics and Pharmacodynamics of Lumasiran

Preclinical and clinical data indicate the renal pathway is a minor elimination route for lumasiran, consistent with the renal excretion properties of 5 other siRNAs with similar physiochemical properties, as detailed below. Hence it is considered that the weight-based dose regimen should be the same regardless of degree of renal function.

A preclinical rat model of renal impairment using lumasiran and 2 additional GalNac conjugated siRNAs showed that renal impairment does not influence the systemic exposure of siRNA, liver PK, or PD (Table 8). The preclinical study used nephrectomized (subtotal nephrectomy) rats, where 5/6th of the kidneys was removed to mimic severe renal impairment. Urinary excretion of siRNAs was reduced to approximately 1% in rats with nephrectomy relative to the 5% renal excretion seen in rats without nephrectomy. However, no meaningful differences were observed in the plasma concentrations, liver PK, and PD of the siRNAs in rats with and without subtotal nephrectomy. Thus, the preclinical study results infer that renal excretion plays a minor role in the disposition of siRNA molecules and that moderate to severe renal impairment does not influence the liver concentration and activity of these molecules.

Table 8: Comparison of PK and PD of siRNAs in Rats with and without Nephrectomy

siRNA	Condition	Plasma[c]		Liver[c]		% Urine Excretion[c]	% mRNA Reduction[c]
		C_{max} (µg/mL)	AUC (h*µg/mL)	C_{max} (µg/g)	AUC (h*µg/g)		
AD-57727[a]	Control	0.161	0.501	14.5	ND	42 ng/mL	74
	Nephrectomy	0.131	0.606	14.6	ND	13 ng/mL	73
AD-68364	Control	0.048	0.198	8	752	5	~70
	Nephrectomy	0.034	0.139	5.8	765	0.74	
Lumasiran[b]	Control	0.080	0.303	11.9	ND	3.2	~70
	Nephrectomy	0.081	0.300	14.7	ND	1.1	~75

Abbreviations**:** AUC=area under curve; mRNA=messenger ribonucleic acid; ND=not determined; siRNA=small interfering RNA

[a] Urine excretion for AD-57727 are reported as concentrations instead of percentage.

[b] Liver concentrations were determined on Day 2 and Day 14, no statistical difference was observed on Day 2, apparent difference in elimination phase (~1.9-fold higher in nephrectomized) on Day 14.

[c] Mean values are reported based on 5 rats.

The contribution of renal excretion to total plasma clearance of lumasiran in humans is low (<25%). This is similar to the renal excretion profiles of other GalNAc conjugated siRNA molecules. The low urinary recovery is attributable to the short plasma circulation time (about 24 hours) for these GalNAc conjugated molecules, including lumasiran. The GalNAc on lumasiran binds to abundantly expressed asialoglycoprotein receptors on hepatocytes leading to highly efficient and rapid uptake of lumasiran from the plasma into hepatocytes. Consequently, plasma concentrations decline rapidly to less than the lower limit of quantitation within 24 to 48 hours postdose.

In addition, a dedicated renal impairment study of a similar GalNAc conjugated siRNA molecule showed that urinary drug excretion accounted for 13.3%, 13.7%, 6.68%, and 3.16 % of that administered study drug in subjects with normal renal function and those with mild, moderate, and severe renal function, respectively. The urine PK data in renal impairment subjects show a small reduction in the already low urinary excretion of siRNA compounds, which suggest up to a 10% increase in liver exposure can be expected in subjects with severe renal impairment compared to those with normal renal function. This indicates that the influence of renal impairment on liver exposures is minimal; hence no major difference in pharmacodynamics is expected in renal impairment patients.

Weight-based Dose Regimen

Lumasiran liver concentration is the sole driver of the pharmacodynamic properties of lumasiran, therefore, change in body weight and liver size particularly during infancy and early childhood (<6 years of age) were considerations that went into dose regimen selection.

The weight-based dosing regimen for this study was informed by preclinical and clinical data of lumasiran (Section 1.2), preclinical data of similar GalNAc conjugated siRNAs, and results of

PK/PD modeling and simulation which considered differences in body weight, liver growth, and metabolic rates.

Data from Study ALN-GO1-001 Parts A and B in healthy subjects and PH1 patients and associated PK/PD modeling were used to support dose selection in adults and children ≥20 kg body weight. The urinary oxalate reductions observed in PH1 patients serve as an indicator of suppression of hepatic oxalate production. Population PK/PD modeling demonstrated dose dependent oxalate reductions over the dose range (1.0 to 6.0 mg/kg continuous once monthly or once every 3 months SC administrations), with diminishing additional effect predicted with higher doses consistent with an asymptotic rather than linear dose-response relationship. For a given dose level, the PK/PD model indicated that monthly administration leads to a more rapid decline in urinary oxalate levels relative to dosing every 3 months. Thus, a lumasiran dosing regimen of 3.0 mg/kg once monthly for 3 loading doses total followed by 3.0 mg/kg once every 3 months was selected for PH1 patients ≥20 kg body weight regardless of renal function status or degree of renal impairment.

The modeling and simulation approach in infants and young children considered the changing rate of body weight and relative liver size in this 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.[CDC 2018; Johnson 2005] For an individual in the 0 to 1 year, 1 to 6 years, and 6 years of 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 although the mg/kg dose is higher in younger patients, the absolute amount (mg) of lumasiran administered is small due to the lower body weight in these younger patients.

Body weight categories for dose selection in this study were determined using CDC growth chart data. Based on PK/PD modeling and simulation, for children with body weight <10 kg, the regimen is 6.0 mg/kg monthly × 3 doses (loading) followed by 3.0 mg/kg monthly (maintenance). For children and adults with body weight ≥10 kg, the regimen consists of a combination of an initial monthly loading dose for the first 3 months, followed by a quarterly maintenance regimen thereafter, as described in Table 9, which also shows the predicted glycolate oxidase suppression per body weight category.

At steady state, these dose regimens are expected to achieve approximately 90% target suppression and reduce hepatic oxalate production to normal or near normal levels. Because renal function is a minor pathway for the elimination of lumasiran, the lumasiran dosing regimen in patients with advanced renal impairment will be the same as in patients with normal renal function.

Table 9: Lumasiran Dosing Regimen in Pediatric and Adult PH1 Patients and Predicted Glycolate Oxidase Target Suppression at Steady State

Body Weight, (kg)	Regimen		Predicted GO Suppression[a], (%)
	Loading	Maintenance	
≥20	3.0 mg/kg qM ×3	3.0 mg/kg q3M	89.7%
10 to <20	6.0 mg/kg qM ×3	6.0 mg/kg q3M	90.2%
<10	6.0 mg/kg qM ×3	3.0 mg/kg qM	86.5%

Abbreviations: GO=glycolate oxidase; h=hour; qM=monthly (every 28 days), q3M=once every 3 months
[a] All values are at steady state.

The physicochemical properties of lumasiran and the available preclinical, clinical, PK, PD, and safety data indicate renal impairment is not expected to influence the systemic exposure, PD, safety, or efficacy properties of lumasiran. Based on these findings the Sponsor has determined that no dose adjustment is required in patients with varying degrees of renal impairment, and the weight-based regimen described in this study is therefore appropriate for patients of all ages with advanced renal disease.

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 complications of systemic 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, disease stage, and status of dialysis dependence.

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. 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 PH1 patients of all ages (infants to adults) with advanced renal disease.

Detailed information about the known and expected benefits and risks of lumasiran are provided in the Investigator's Brochure.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Cohort A • Evaluate the effect of lumasiran on plasma oxalate in patients who are not on dialysis therapy **Cohort B** • Evaluate the effect of lumasiran on plasma oxalate levels in patients who are on dialysis therapy	**Cohort A** • Percent change in plasma oxalate from Baseline to Month 6 **Cohort B** • Percent change in pre-dialysis plasma oxalate from Baseline to Month 6
Secondary	
• Evaluate the effect of lumasiran on change in plasma oxalate area under the curve (AUC) between dialysis sessions • Evaluate the long-term effects of lumasiran on change in plasma oxalate • Evaluate the effect of lumasiran on change in urinary oxalate excretion • Evaluate quality of life in patients with PH1 • Characterize the PK of lumasiran • Evaluate the effect of lumasiran on nephrocalcinosis • Evaluate the effect of lumasiran on dialysis requirements • Evaluate the effect of lumasiran on the occurrence of renal stones	<u>Primary Analysis Period (Baseline to 6 months)</u> • Percent change in plasma oxalate AUC between dialysis sessions • Absolute change in plasma oxalate • Change in the following parameters: o Urinary oxalate

Objectives	Endpoints
• Evaluate the effect of lumasiran on renal function • Evaluate the effect of lumasiran on change in measures of systemic oxalosis	○ QoL assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent • Plasma PK parameters of lumasiran <u>Long-term Extension Period (6 months to end of study)</u> • Percent change in plasma oxalate AUC between dialysis sessions • Percent and absolute change in plasma oxalate • Change in the following parameters: ○ Nephrocalcinosis as assessed by renal ultrasound ○ Frequency and mode of dialysis ○ Frequency of renal stone events ○ Urinary oxalate ○ Renal function as assessed by eGFR ○ Measures of systemic oxalosis in the following systems: ▪ Cardiac ▪ Dermatologic ▪ Skeletal ▪ Ocular ○ QoL(Quality of life) assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent
Exploratory	
• Evaluate growth parameters and developmental milestones in patients who are <6 years of age at consent • Evaluate quality of life in patients with PH1 • Evaluate the effects of lumasiran on patient and caregiver resource use	• Growth parameters in patients who are <6 years of age at consent • Change in developmental milestones over time in patients <6 years of age at consent • Change in QoL as assessed by EQ-5D-Y and PedsQL (individual subscales of the generic and ESRD modules, and ESRD module total

Objectives	Endpoints
• Describe patient experiences on lumasiran in PH1 patients and the experiences of caregivers for these patients • Assess for antidrug antibodies (ADA) against lumasiran • Evaluate the effects of lumasiran on additional pharmacodynamic (PD) parameters of plasma glycolate and urinary glycolate	score) for patients ≥2 to 18 years of age at consent, and as assessed by EQ-5D-5L in patients ≥18 years of age at consent • Change in QoL as assessed by KDQOL Symptoms and Problems of Kidney Disease subscale in patients ≥18 years of age at consent • Change in patient and caregiver resource use (eg, work/school attendance, visits to doctor/hospital) • Change in patient and caregiver experiences as evaluated by a patient experience questionnaire and a caregiver experience questionnaire • Frequency of ADA • Change in urinary and plasma glycolate
Safety	
• Evaluate the safety and tolerability of lumasiran	• Frequency of adverse events

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, single arm study designed to evaluate the efficacy, safety, PK and PD of lumasiran in patients with a documented diagnosis of PH1 who have advanced renal disease, as evident by eGFR ≤45 ml/min/1.73 m^2. All eligible patients will be administered lumasiran; no control group will be assessed.

This study will include 2 cohorts: Cohort A and Cohort B. Cohort A will include patients who do not yet require dialysis. Cohort B will include patients who are on dialysis therapy. Dialysis modality will be restricted to patients on hemodialysis. Patients on a combination of peritoneal and hemodialysis, and patients on peritoneal dialysis only will be excluded from the study. Enrollment to both cohorts will occur concurrently. Cohort A patients who experience progression of renal impairment over time and begin to require dialysis therapy will cross-over to Cohort B.

Patients will be screened from Day -120 to Day -1 to determine eligibility. Consented patients meeting all eligibility criteria will receive their first dose of lumasiran on Day 1. Lumasiran will be administered subcutaneously (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, and PK, and other procedures 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. Dialysis status and changes in dialysis regimen will be monitored. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, visits by a healthcare professional may occur at an offsite location such as the patient's home).

Blood samples will be collected in both cohorts for PK parameter analysis, plasma oxalate sample analysis, and to establish plasma oxalate profiles (in Cohort B only; the profile enables AUC calculation between dialysis sessions) (Table 5, Table 6). From Screening to Day 1, patients will have at least 4 plasma oxalate collections (pre-dialysis in Cohort B) to establish a robust baseline measurement. The plasma oxalate sample collection during Screening is described per cohort in Figure 1, and during the treatment period will be performed as per the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4).

Patients who are anuric are defined as producing <100 ml of urine per day. For all patients who are not anuric (ie, can produce ≥100 ml of urine per day), single-void urine samples (in triplicate) will be collected during screening to establish baseline and then serially per the Schedules of Assessments.

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 dose. There will be a single 24-hour urine collection at Month 3, Month 12, and every 6 months thereafter while on study.

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 as described in Section 4.3.1.

3.2. Duration of Treatment

The duration of treatment with lumasiran is up to 60 months, with final dose administered at the Month 57 visit.

3.3. Duration of Study

The estimated total time on study, inclusive of screening, for each patient is up to 64 months, including up to 120 days 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 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 6 patients in each cohort. Of those 20 patients, the planned enrollment includes 4 patients who are <6 years of age at consent, and 2 patients between ≥6 to <18 years of age at consent.

Patients who crossover from Cohort A to Cohort B (due to progressing to dialysis therapy), discontinue study drug, or stop participation in the study prior to completion of Month 6 assessments may be replaced (see Section 4.3.4).

3.5. Method of Assigning Patients to Treatment Groups

Patients will all be assigned to 1 single treatment group. 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.

3.6. Blinding

Not applicable.

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. Additional assessments may be recommended by the DMC. 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:

4.1.1. Cohorts A and B

Age

1. Have reached at least 37 weeks estimated gestational age (full-term infant) at consent (or assent).

Patient and Disease Characteristics

2. Documentation or confirmation of PH1 as determined by genetic analysis prior to initial dosing.
3. Patients with eGFR ≤45 mL/min/1.73 m^2 as calculated by the MDRD formula if ≥18 years or Schwartz Bedside Formula if ≥12 months to <18 years, or patients <12 months of age with serum creatinine that is considered elevated for age at consent.

4. The mean of the three most recent screening plasma oxalate samples collected prior to Day 1 is ≥20 µmol/L. In Cohort B, these 3 collections may include the first pre-dialysis sample from each plasma oxalate profile.
5. If taking therapeutic vitamin B6 (pyridoxine), must have been on stable regimen for at least 90 days before consent, and is able and willing to remain on this stable regimen until at least the Month 6 visit. Dose adjustments for interval weight gain are acceptable.

Informed Consent

6. Patient is willing and able to comply with the study requirements and to provide written informed consent. In the case of patients under the age of legal consent, the legal guardian(s) must provide informed consent and the patient should provide assent per local and national requirements.

4.1.2. Cohort B Only

1. On a stable hemodialysis regimen for at least 4 weeks prior to Screening plasma oxalate assessment; able and willing to maintain this regimen through Month 6 visit, with changes to dialysis regimen permitted only when medically indicated.

4.2. Exclusion Criteria (Cohorts A and B)

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

Laboratory Assessments

1. Has any of the following laboratory parameter assessments at Screening:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2× ULN for age
   b. Total bilirubin >1.5×ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2× ULN
   c. International normalized ratio (INR) >1.5 for patients not on anticoagulants. Patients on oral anticoagulants (eg, warfarin) with an INR <3.5 will be allowed.
   d. Hemoglobin <8.0 g/dL
2. Has known active human immunodeficiency virus (HIV) infection; or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B (HBV) infection.

Prior/Concomitant Therapy

3. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study during Screening. Consultation with the Medical Monitor is required if treated with unapproved products prior to consent regardless of the time interval prior to the first dose of study drug.

Medical Conditions

4. Known history of allergic reaction to an oligonucleotide or GalNAc.
5. Diagnosis of conditions other than PH1 contributing to renal insufficiency such as glomerulonephritis, nephrotic syndrome, or lupus nephritis.

6. Any condition or comorbidity, which in the opinion of the Investigator, would make the patient unsuitable for dosing or would interfere with study compliance, data interpretation, patient safety, and/or patient participation in the study. This includes significant active and poorly controlled (unstable) cardiovascular, neurologic, gastrointestinal, endocrine, renal or psychiatric disorders unrelated to PH1 identified by key laboratory abnormalities or medical history.
7. Unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol intake of >2 units/day is excluded during the study (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL].
8. History of alcohol abuse, within the last 12 months before screening, in the opinion of the investigator.
9. Patients with a previous liver transplant or for whom a liver transplant is anticipated in the next 6 months.
10. Patients with a previous kidney transplant who are currently receiving immunosuppression to prevent transplant rejection.
11. Patients maintained on a peritoneal dialysis regimen.
12. Patients who in the opinion of the Investigator plan to start dialysis replacement therapy in the next 6 months.
13. Any comorbidity or condition that, in the opinion of the Investigator, is anticipated to prevent participation in at least 12 months of the study.

Contraception, Pregnancy, and Breastfeeding

14. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.5.1.
15. Female patient is pregnant, planning a pregnancy, or breast feeding.

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 may 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

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. 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.

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 primary analysis 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.

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.

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 prior to the Month 6 visit 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 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 countries where permitted.

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 through Month 6 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 by 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 or designee should 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. Patients who crossover from Cohort A to Cohort B due to progressing to dialysis prior to Month 6 also may be replaced at the Sponsor's discretion. 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 10. Liver function test clinical laboratory assessments (see Table 13) from the Week 2 visit must be reviewed prior to administration of the Month 1 dose, as specified in the Schedules of Assessments (Table 1). The LFT criteria for withholding, monitoring, or stopping dosing is described in Section 5.2.3.1. 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. Study drug administration must be at least 21 days apart. In patients on dialysis therapy, study drug should be administered as soon as feasible following the end of dialysis, ie, no later than 120 minutes post-dialysis.

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 patient or patient's 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 patient/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.

In addition, assessments specific to measures of systemic oxalosis (eg, observing and photographing skin lesions during physical examinations) must be performed at the study center for the duration of the study, as specified in the Schedules of Assessments (Table 1, Table 2 Table 3, Table 4).

Table 10: 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 <6 years of age, the dose will be based on a weight obtained within 7 days prior to dosing. In patients ≥6 years of age, body weight collected within 3 months prior to the study drug dose or the predose weight collected on the study visit day or dosing day will be used for dose calculations.

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 dose will be based on weight obtained within 6 weeks prior to dosing for patients who are <10 kg and within 4 months for patients who weigh ≥10 kg. For Cohort B patients, if a post dialysis weight taken at the study

center is not available within the specified timepoints, post dialysis weight taken at the dialysis center may be used.

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).

Additional details can be found in the Pharmacy Manual. In addition, instructions and procedures related to the administration of lumasiran by a patient or 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. Liver function test (LFT) results (see Table 13) 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 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. 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.
2. For any ALT or AST elevation >3× ULN, central laboratory results should be used to guide subsequent monitoring as detailed in Table 11.
3. 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 11 and Table 14.

4. 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.
5. 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 11.

Table 11: 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 14 (all assessments to be performed; see Section 6.5.5.4 for guidance on maximal pediatric blood volumes)
	  • Hematology, serum chemistry, and LFT per Table 13
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor at least every two weeks: LFT per Table 13
	• 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 14 (all assessments to be performed once)
	  • Hematology, serum chemistry, and LFT per Table 13
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor at least weekly: LFT per Table 13 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. See the Study Manual for sample priority list.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or 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 Assessments (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 or dialysis regimen 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 and dialysis maintenance as determined by treating physician. Patients should continue their current standard of care and dialysis regimen, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy at least until the Month 6 visit. Changes in dialysis regimen may be permitted only if medically indicated. 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 Assessments (see Table 1, Table 2, Table 3, and Table 4). 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 of child-bearing potential must be willing to use a highly effective method of contraception from 14 days before first dose, throughout study participation, and for 90 days after last dose administration or until study completion. Pediatric/adolescent female patients must initiate one of the birth control methods below, which includes true abstinence, at menarche or must discontinue study drug.

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.

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone level within the postmenopausal range.

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. Males with partners of child-bearing potential must agree to use a condom throughout study participation and for 90 days after the last dose of study drug or until study completion.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study. 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.

Urine collection assessments are not required for patients who are anuric (ie, produce <100 ml per day).

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, length/height and weight, an abbreviated physical examination/body system assessment, and preparation and administration of study drug (at the discretion of the Investigator).

6.1. Screening Assessments

The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given COVID-19 limitations.

An informed consent form (ICF) or assent form in the case of patients under the age of legal consent that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient (or legal guardian if under the age of legal consent) before the Screening procedures are initiated. All patients (or their legal guardians if under the age of legal consent) will be given a copy of the signed and dated ICF and/or assent form. In the case when a patient reaches the legal age of consent during the study, the Investigator must obtain the patient's informed consent, and assent if applicable, prior to performing any further study interventions and/or procedures involving that patient (see Section 8.1.1).

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria (see Section 4.1 and Section 4.2). 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.

For all patients who are not anuric, single-void urine samples (in triplicate) will be collected during screening to establish baseline. Also, in patients who are able to produce urine, 24-hour collections will be performed during Screening to establish baseline urinary oxalate levels (Section 6.1.2).

The timing of samples collected during Screening for plasma oxalate and plasma glycolate will be as shown in Figure 1.

The three most recent screening plasma oxalate samples collected prior to Day 1, which may include the pre-dialysis sample from the plasma oxalate profile collection for Cohort B patients, will be used to assess eligibility. If all 3 plasma oxalate assessments are obtained >60 days prior to Day 1, one additional plasma oxalate will be performed (at least 7 days prior to Day 1).

For subjects in Cohort B, there must be 2 separate plasma oxalate profile assessments performed during Screening, performed at least 1 week apart.

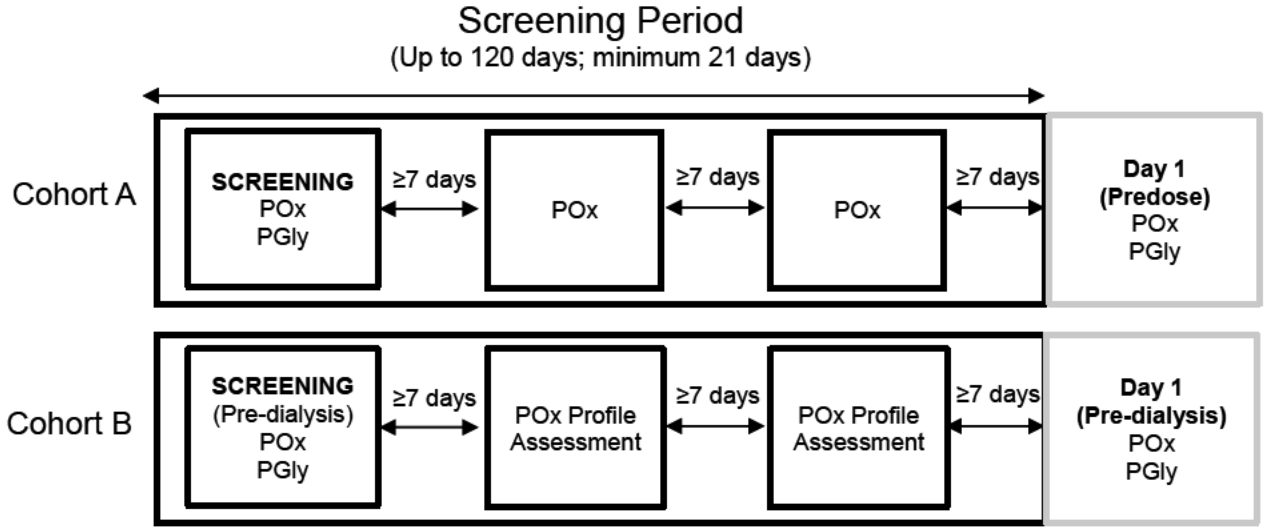
If a patient's stable dialysis regimen at the time of consent is interrupted during screening for ≤14 days, plasma oxalate levels should not be collected until the prior dialysis regimen has resumed for at least 2 weeks. If a patient's stable dialysis regimen at the time of consent is

interrupted for >14 days, plasma oxalate should not be collected until the stable dialysis regimen has resumed for at least 4 weeks.

If a patient's stable dialysis regimen at the time of consent is permanently changed during screening, plasma oxalate should not be collected until the new dialysis regimen has been established for at least 4 weeks. Any plasma oxalate profiles and pre-dialysis plasma oxalate samples collected prior to this point will not be used for the study. A total of 2 plasma oxalate profiles and a pre-dialysis plasma oxalate sample need to be collected AFTER the new stable dialysis regimen has been established for at least 4 weeks.

Plasma glycolate assessments should be done twice: once with the initial screening assessments and again on Day 1 prior to dosing. Results of the plasma glycolate assessments are not required prior to dosing.

Figure 1: Minimum Blood Sample Collection for PD Assessments During Screening



Abbreviations: POx=plasma oxalate; PGly=plasma glycolate.
Note, POx Profile Assessment is the area under the curve (AUC) between dialysis sessions; see Table 6 for POx Profile Assessment blood sample time points.

6.1.1. Retesting

If in the Investigator's judgement, the screening laboratory abnormalities are likely to be transient, then laboratory tests may be repeated. The Investigator's rationale should be documented. Laboratory values can be retested once during Screening after consultation with the Medical Monitor, provided that the patient can be evaluated for eligibility within the Screening period.

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria may be allowed to return for rescreening after consultation with the Medical Monitor. The patient or legal guardian (if applicable) will be re-consented, and assent obtained (if applicable) if rescreening occurs outside of the 120-day screening window. If patients require rescreening, screening assessments previously obtained within 120 days prior to Day 1 may be used. In addition, X-rays, bone scans, ophthalmologic

examinations, exploratory DNA assessments, and blood and urine samples for exploratory analyses obtained within 120 days of Day 1 do not need to be repeated. Echocardiogram and ECG will be repeated if obtained 60 or more days prior to Day 1.

6.2. Efficacy Assessments

The efficacy of lumasiran will be assessed in all patients in both cohorts by evaluating changes in plasma oxalate levels; and plasma oxalate profile assessment in Cohort B only (Section 6.2.1); urinary oxalate (in non-anuric patients, Section 6.2.2), and measures of systemic oxalosis (Section 6.2.3).

In Cohort A patients, all blood and urine samples will be collected predose, when applicable. In Cohort B patients with a dialysis session on the day of dosing, samples will be collected prior to the dialysis session.

The efficacy of lumasiran on renal function will be assessed by eGFR (Section 6.3.4).

Change in the frequency and mode of dialysis will be assessed (Section 6.5.5.5).

In both cohorts, change in levels of urinary and plasma glycolate will be assessed.

6.2.1. Plasma Oxalate

Plasma oxalate levels will be assessed from blood samples collected in all patients; levels will be measured via central laboratory using a validated assay. The collection timing during Screening is detailed by cohort in Figure 1. During the treatment period, samples will be collected as specified in the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4) and in Table 6.

6.2.1.1. Cohort A

In Cohort A patients, plasma oxalate levels will be assessed via blood samples collected throughout the study as specified in the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4). The three most recent screening plasma oxalate samples collected prior to Day 1 will be used to assess eligibility; see Section 6.1 and Figure 1.

6.2.1.2. Cohort B

Plasma Oxalate Level

In Cohort B patients, plasma oxalate levels will be assessed via pre-dialysis blood samples collected throughout the study as specified in the Schedules of Assessments. From Screening to Day 1, at least 4 pre-dialysis blood samples obtained at least 7 days apart over the span of at least 28 days will be collected to assess eligibility. Up to 2 of the blood samples may originate from the pre-dialysis samples collected at the beginning of the plasma oxalate profile assessments performed during Screening (described below). See Figure 1.

Plasma Oxalate Profile

Plasma oxalate profiles will be performed as specified in the Schedules of Assessments to permit calculation of the AUC between dialysis sessions. The plasma oxalate profile assessment consists of an overnight visit requiring collection of up to 8 blood samples for plasma oxalate over the course of a 24-hour span, dependent on blood volume limitations and study center

facilities; blood sample collection schedule is described in Table 6, which includes collections before, during, and after the dialysis session. During Screening, there will be 2 separate profile assessments performed at least 7 days apart. See Figure 1.

During Screening, the blood sample timepoints described in Table 6 are relative to when dialysis is performed. During the treatment period, the timepoints described in Table 6 are relative to dialysis or when the dose is administered, as specified. The 24-hour postdose sample will be collected prior to beginning the next hemodialysis session, or 24 hours (±3 hours) postdose if there is no hemodialysis session on the day following dosing.

In patients with ≥1 systemic oxalosis manifestation during the study, additional plasma oxalate profile assessments will be performed at the Month 36 and Month 48 visits, and blood sample collection timepoints are the same as described above.

6.2.2. Urinary Oxalate

In patients in both Cohort A and Cohort B who are not anuric (ie, patients who are able to continue to produce urine ≥100 ml per day) and are able to complete the collection procedure, 24-hour urinary oxalate excretion will be assessed. 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 who are not anuric. Table 12 shows the 24-hour urine collection procedure by study visit.

In patients 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. 24-hour urine collections in patients not undergoing dialysis must meet pre-specified validity criteria (see Section 6.2.2.1).

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 dose to evaluate changes in oxalate concentrations over the 6-month interval. A single 24-hour collection will be scheduled at Month 3, Month 12, and then every 6 months thereafter as specified in the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4). In patients undergoing dialysis, the timing of the collections relative to patients' weekly dialysis schedule should remain consistent for each patient, when possible.

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.

All patients who are not anuric will have 3 single-void urine samples collected during Screening (first morning voids are preferred, when feasible). Following screening, single-void collections are performed within 7 days predose, as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). Samples may be collected as an outpatient prior to the visit or collected during the study visit prior to dosing, as applicable.

Table 12: 24-hour Urine Collection Procedure by Study Visit for Patients who are not Anuric

Study Visit and 24-hour Urine Collection Window	Number of 24-hour Collections	Notes
Screening (within 120-day period prior to initial dosing)	3 voided collections	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	Supervised 24-hour collections are encouraged unless patient/caregiver already familiar with collection procedure.
Months 3, 12, and every 6 months through end of study	1 voided collection	--

6.2.2.1. Validity Criteria for 24-hour Urine Collections

Detailed instructions on 24-hour urine collections will be provided to patients or caregivers. 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.
- In patients not undergoing dialysis, the 24-hour creatinine content is at least 5 mg/kg for patients <6 years of age, and 10 mg/kg for patients ≥6 years of age, as assessed by the study central laboratory.

In patients undergoing dialysis, 24-hour collections are not required to have a minimum creatinine content to be considered valid.

6.2.3. Measures of Systemic Oxalosis

As measures of the PD effect of lumasiran on systemic oxalosis, cardiac, dermatologic, skeletal, and ocular measures of oxalosis will be assessed in all patients where feasible according to age and where local IRB/IEC permits.

6.2.3.1. Cardiac

To assess the effect of lumasiran on cardiac outcomes driven by systemic oxalosis, echocardiograms will be performed; echocardiogram acquisition time will be standardized relative to dialysis session when applicable. Parameters to be followed include features of infiltrative cardiomyopathy including cardiac structure and function. Echocardiogram acquisition will be standardized and detailed in the study manual. Echocardiograms will be read centrally.

In addition to safety assessments described in Section 6.5.4, as a measure of systemic oxalosis, ECGs will be monitored to identify conduction disorders if normal at baseline or change in conduction disorders if present at baseline.

Triplicate 12-lead ECGs will be collected using standardized machines 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 2 months after the Month 3 timepoint, up to 5 months after the Month 6 timepoint, and up to 11 months after the Month 12 timepoint. 12-lead ECGs will be centrally read.

6.2.3.2. Dermatologic

In cases where skin manifestations due to systemic oxalosis are reported during the course of the study, (eg, patient presenting with skin lesion during physical examination) photographs of the lesions should be obtained. The Investigator may engage a local dermatologist's opinion if required. When a skin manifestation of systemic oxalosis is observed, at each succeeding visit, photographs of the affected area will continue to be collected to record the resolution or worsening of the manifestation. Further details will be provided in the study manual.

6.2.3.3. Skeletal

Radiographs (X-rays) of hands, hip, knee, and chest will be obtained and read centrally for features of skeletal oxalosis, where local IRB/IEC permits at the timepoints specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4), where feasible based on patient compliance. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, X-rays may be completed up to 1 month after Day 1, and up to 11 months after the Month 12 timepoint.

Only a subset of these x-rays will be collected at selected study centers. In addition, a reading of bone age will be performed for patients who have not yet reached skeletal maturity. Results will be interpreted using a scale developed in conjunction with the central reading core laboratory, as detailed in the study manual.

Optional bone scans will be performed in only Cohort B patients ≥18 years of age to assess calcium oxalate systemic deposition, where local IRB/EC permits and if patient consents to the bone scan. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, optional bone scans may be completed up to 1 month after Day 1, and up to 11 months after the Month 12 timepoint.

6.2.3.4. Ocular

Ophthalmology

The following ophthalmologic exams will be performed: Color Fundus Photography (CFP), Optical Coherence Tomography (OCT), and, where available at select sites, Fundus Autofluorescence (FAF).

Ophthalmologic exams with fundus photography will be standardized and the fundus photographs will be read centrally. OCT assessments will also be standardized and read centrally. For young children unable to cooperate, examinations will be optional. Anesthesia

will not be used in any of these ocular assessments. Results from any clinically obtained exams performed as standard of care may be collected.

During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, ophthalmologic exams may be completed up to 1 month after Day 1, and up to 11 months after the Month 12 timepoint.

Best Corrected Visual Acuity (BCVA)

Where available, BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts will be assessed longitudinally throughout the course of the study to evaluate for changes which correspond to changes in retinal oxalate deposition. Exams will be standardized across applicable sites. In younger patients <6 years of age, alternate visual acuity testing per local standard practice may be performed (eg, LEA symbols). In sites where ETDRS testing is not available, Snellen or LEA symbol charts may be used for BCVA. Testing is not required in preverbal infants.

6.3. Renal Assessments and Additional Pharmacodynamic Measurements

Renal assessments and additional pharmacodynamic assessments include: nephrocalcinosis as assessed by renal ultrasound (Section 6.3.1); frequency of renal stone events (Section 6.3.2); urine oxalate:creatinine ratio (in available urine collections; Section 6.3.3); and eGFR (Section 6.3.4).

Glycolate concentrations may be collected at the same time as the plasma oxalate sample collection (Section 6.2.1) as specified for Screening (Figure 1) and as per the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4). Additional collections may be performed at the discretion of the Investigator.

In Cohort A patients, all samples will be collected predose, when applicable. In Cohort B patients with a dialysis session on the day of dosing, samples will be collected prior to the dialysis session.

All PD assessments will be analyzed centrally. 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. Renal Ultrasound

Renal ultrasounds will be obtained locally, as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4) when feasible; anephric patients are exempt from renal ultrasound assessments. Renal ultrasound will be performed according to instructions provided in the Study Manual in a standardized manner. Renal ultrasounds will be reviewed centrally.

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 1 month after Day 1, up to 5 months after the intended timepoint for assessments scheduled prior to Month 12, and up to 11 months after the intended timepoint for visits at Month 12 and subsequent timepoints, if necessary.

6.3.2. 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).

6.3.3. Urinary Oxalate:Creatinine Ratio

Urine oxalate:creatinine ratios will be calculated from the oxalate and creatinine levels measured in the available 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.

6.3.4. Estimated Glomerular Filtration Rate

In patients not undergoing dialysis, blood samples for the assessment of eGFR (mL/min/1.73 m^2) will be obtained at the time points specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4).

In patients ≥12 months to <18 years at consent, eGFR will be calculated based on the Schwartz Bedside Formula [Schwartz 2009] (Appendix 10.1). In patients ≥18 years of age at consent, eGFR will be calculated based on the Modification of Diet in Renal Disease (MDRD) formula. [Levey 2009; Schwartz 2009]

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 in patients in Cohort A is provided in Table 5. In patients who are able to produce urine, a urine sample for PK analysis will be collected as on Day 1.

Also, a detailed schedule of time points for the collection of blood samples for PK analysis in Cohort B patients is provided in Table 6. Plasma oxalate profile assessment during Screening

should be conducted as explained in Section 6.2.1. PK and plasma oxalate blood samples should be collected before the start of the next dialysis session.

In patients who are not on dialysis at consent but start dialysis prior to Month 6 visit, PK and plasma oxalates blood samples should be collected as per Table 6 at the next scheduled protocol assessment in the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4) and then continue per the timepoints in Table 6 for the rest of the study.

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 limits permit (see Section 6.5.5.4).

Lumasiran plasma concentrations will be determined using a central laboratory with a validated assay. Details regarding sample volumes to be collected, sample processing, and shipping 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 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 will be recorded in the eCRF. 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 for patients <18 years of age.

Body weight will be measured in kilograms. In patients <6 years of age, body weight will be obtained within 7 days of dosing. In Cohort B patients, body weight will be obtained post-dialysis. In patients ≥6 years of age, body weight collected within 3 months prior to the study drug dose or the predose weight collected on the study visit day or dosing day will be used for dose calculations (see Section 5.2.2).

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. In Cohort B patients, the physical examination should be conducted after dialysis is completed. 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 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. Abnormal findings from dermatological examinations will be recorded via photography (see Section 6.2.3.2).

6.5.4. Electrocardiogram

Triplicate 12-lead ECGs will be obtained predose, when applicable, as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4). Electrocardiograms may be completed up to 2 months after the Month 3 timepoint, up to 5 months after the Month 6 timepoint, and up to 11 months after the Month 12 timepoint. 12-lead ECGs will be centrally 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, if feasible.

Qualified staff 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.

ECGs will be utilized as secondary endpoints of the pharmacodynamic effect of lumasiran on systemic oxalosis, as described in Section 6.2.3.1.

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. 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. Clinical laboratory assessments are listed in Table 13 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 decisions, on the day of visit assessments, all laboratory assessments specified in Table 13 which are performed at a local laboratory should also be sent in parallel to the 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. 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.

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 13: 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 (Bedside Schwartz formula for children ≥12 months to <18 years of age at consent; MDRD formula for adults ≥18 years of age at consent)	Chloride
Pyridoxine (vitamin B6)[a]	
Liver Function Tests	
AST	ALP
ALT	Serum bilirubin (total and direct)
Urinalysis[b]	
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.

[b] Urinalysis will not be collected in Cohort B patients who are anuric (ie, produce <100 ml of urine per day).

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 females of child-bearing potential, and for pediatric/adolescent females upon initiation of menarche. A serum pregnancy test will be performed at Screening and at the first visit after initiation of menarche, if applicable, and serum or urine pregnancy tests will be performed thereafter per the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4) and any time pregnancy is suspected. A serum pregnancy test will be performed in lieu of a urine pregnancy test in Cohort B patients who are anuric (ie, produce <100 ml of urine per day). Pregnancy testing may be performed offsite by a patient or patient's caregiver if a patient/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 are pregnant at Screening are not eligible for study participation. Patients with a positive urine pregnancy test, subsequently confirmed by a positive serum 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 at least until the pregnancy outcome is known (see Section 6.5.6.7 for follow-up instructions).

Follicle-stimulating hormone testing may be performed to confirm suspected post-menopausal status.

6.5.5.3. Additional Liver Function Assessments

LFT results should be assessed and reviewed 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 (ie, >3 × ULN) without an alternative cause or other LFT abnormalities per central laboratory, and as per the blood draw priority list, all assessments in Table 14 will be performed one time, as well as hematology, serum chemistry, and LFT assessments from Table 13, 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; assessments described below may be staggered accordingly due to blood volume limitations.

Monitoring, including criteria for dose modification or withholding the study drug, is described in 5.2.3.1.

Table 14: 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:

- Assessments will be measured in central laboratory or locally when not feasible to conduct centrally, ie, in very young patients. 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 15 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.

6.5.5.5. Dialysis Parameters

Dialysis modality evaluations will be performed in all patients in Cohort B. To prevent potential confounding of study results for the primary analysis, elective changes to dialysis regimen are not permitted during Screening or the 6-month primary analysis period, ie, decreasing dialysis frequency in response to lowered plasma oxalate, or elective changes to dialysis frequency, duration, filter size or type, and blood flow. Changes in dialysis due to management of renal failure (eg, electrolyte content, fluid withdrawal settings), will be performed throughout the study according to Investigator judgement in consultation with the patient's treating physician.

Dialysis parameters may include, but are not limited to, duration and frequency. The dialysis regimen will be monitored according to the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4).

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 6.3.2) 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 (Section 6.5.6.1), the Sponsor or its designee should be notified within 24 hours using the appropriate 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 by a legal guardian or caregiver in approximately 20 to 60 minutes.

6.8. Quality of Life Questionnaires

For QOL instruments described below, they will be assessed where available, and all will be carried forward throughout the study duration as patient age advances to qualify for each succeeding age-specific instrument, as appropriate. The surveys and questionnaires described below will be completed at the timepoints specified in the Schedules of Assessments (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.

6.8.1. EQ-5D

The EQ-5D is a standardized instrument for use as a measure of QOL outcome.[Herdman 2011] It consists of a questionnaire pertaining to 5 dimensions. There is also a visual analog scale, scoring of which is based on a visual scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Higher scores indicate better health status. Patients ≥18 years of age at time of assessment will complete the EQ-5D adult version of the questionnaire using the 5-level (5L) value set, and patients ≥2 to <18 years of age at time of assessment will complete the youth version of this questionnaire, the EQ-5D-Y. Legal guardians may complete questionnaires on behalf of younger infant to pediatric patients, as appropriate.

6.8.2. PedsQL

Peds-QL is a modular approach to measuring QOL in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL Generic Core Scales contain 23 items designed to measure core domains of health (physical, emotional, and social functioning) and

role (school functioning). Scores are summarized as Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score. The Total Scale Score, individual subscales of the generic and ESRD modules (parent and/or self-report versions), and ESRD module total score will be assessed for this study. The PedsQL will be completed by patients (or caregivers, as appropriate) who are ≥2 to <18 years of age at the time of consent.

6.8.3. KDQOL

The Kidney Disease and Quality of Life (KDQOL-36) questionnaire is used to assess 3 core domains of kidney disease including: burden, symptoms/problems, and effects of kidney disease on daily life. The KDQOL subscales (Burden of Kidney Disease, Effect of Kidney Disease on Daily Life, and Symptoms and Problems of Kidney Disease), and the accompanying Short Form-12 (SF-12) Physical Component Summary and Mental Component Summary will be assessed for this study. These will be completed by patients who are ≥18 years of age at the time of consent.

6.9. Patient/Caregiver Experience Surveys and Impact Questionnaires

The surveys and questionnaires described below will be completed at the time points specified in the Schedules of Assessments (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.

6.9.1. Patient Experience Survey

The Patient Experience Survey assesses patients' experience living with PH1, including their experience with PH1 treatments.

Patients ≥13 years of age at screening will complete the survey unaided if they are able. If the patient is unable to complete the Patient Experience Survey alone, their caregiver or study site staff may complete the survey on behalf of the patient. If the patient is <13 years of age at screening, a caregiver will complete the Patient Experience Survey on behalf of the patient for as long as the patient remains under the legal age of consent.

6.9.2. Caregiver Experience Survey

The Caregiver Experience Survey assesses the consequences of PH1 on caregivers of PH1 patients.

Caregivers of patients under legal age of consent at the time of Screening will be asked to complete the Caregiver Experience Survey. For patients who reach the legal age of consent per local regulations during the study, caregivers will be encouraged to continue completing the survey, but are not required to do so. Caregivers of patients over the legal age of consent at the time of Screening will also be encouraged to complete the survey according to the Schedule of Assessments, but are not required to do so.

6.9.3. Patient and Caregiver Impact Questionnaire

The patient and caregiver impact questionnaire will be used to assess impacts of PH1 on the patients' lives, including their need to relocate/travel to receive treatment, the number and type

of healthcare providers they use, and their ability to work and/or go to school. The questionnaire will also assess the impact on caregivers' employment and/or education.

Patients ≥13 years of age at screening will complete the questionnaire unaided if they are able. If the patient is unable to complete the survey alone, their caregiver or site staff may complete the survey on the patient's behalf. If the patient is <13 years of age at Screening, a caregiver will complete the questionnaire on behalf of the patient. For patients who reach the legal age of consent per local regulations during the study, and whose caregivers had previously completed the Patient Impact Questionnaire on their behalf, caregivers will be encouraged to continue completing the questionnaire, but are not required to do so.

6.10. Healthcare Resource Utilization

Healthcare resource utilization will be assessed using patient or caregiver-reported information related to all hospitalizations, urgent healthcare visits, procedures and surgeries, and collected as specified in the Schedules of Assessments (see Table 1, Table 2, Table 3, and Table 4).

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before the dosing of the first patient in this study. 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, including at least 6 patients in each cohort. Of those 20 patients, the planned enrollment includes 4 patients <6 years of age at consent, and 2 patients between ≥6 to <18 years of age at consent. The sample size was determined based on feasibility considerations, not power calculations.

7.2. Statistical Methodology

Statistical analyses will be primarily descriptive. Summary statistics and by-patient listings/by-patient figures will be presented. Summaries for efficacy will be based on the Efficacy Analysis Set and safety endpoints will be based upon the Safety Analysis Set (Section 7.2.1).

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 lumasiran during the study.

- Efficacy Analysis Set: All patients who received any amount of lumasiran and have at least 1 valid plasma oxalate value at baseline and at the Month 3 assessment or beyond.
- PK Analysis Set: All patients who received any amount of lumasiran have at least 1 postdose blood sample for PK parameters and have evaluable PK data.

The primary population used to evaluate efficacy will be the Efficacy Analysis Set and safety will be the Safety Analysis Set. 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

Every effort will be made to minimize the amount of missing data in the study. Patients who discontinue the study prior to Month 6 will be encouraged to remain on study and complete their remaining clinical visits (excluding PK assessments) through the Month 6 visit and only safety follow-up visits afterwards. Details about 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

There will be a Primary Analysis Period for Cohort A, and separately for Cohort B. There will not be an interim analysis prior to at least 1 cohort completing the Primary Analysis Period.

7.2.5.1. Primary Endpoint

In Cohort A patients, the plasma oxalate baseline is defined as the mean of the last 4 plasma oxalate level values collected prior to the first dose of lumasiran. In Cohort B patients, the plasma oxalate baseline is similarly defined except that the values obtained from the plasma oxalate profile assessment visits will only include the first pre-dialysis sample collected per visit.

The primary analysis is percent change from baseline in plasma oxalate (Cohort A) / pre-dialysis plasma oxalate (Cohort B) summarized Month 3 through Month 6 by cohorts.

For patients who crossover from Cohort A at baseline to Cohort B before Month 6, due to initiation of dialysis between Day 1 and the Month 6 assessments, descriptive listing and figures will be provided.

Percent change in plasma oxalate from baseline (pre-dialysis levels in Cohort B) will be summarized through Month 6. Further details will be included in the SAP.

7.2.5.2. Secondary Endpoints

Secondary endpoints will be analyzed and reported with by-patient listings and by-patient figures of actual values, change from baseline and percent change (where appropriate per endpoint) at

each visit (scheduled and unscheduled visits). Tabular summaries using descriptive statistics (mean, standard error, median, min, max) will be reported. For binary endpoints, the number and percentages of patients in each category will be displayed at each visit. Other subgroup analyses may be generated if applicable.

For patients in Cohort B, the secondary endpoint of percent change from baseline in plasma oxalate AUC will be summarized through the Month 6 plasma oxalate profile assessment. Baseline plasma oxalate AUC measurement will be obtained via the plasma oxalate profile assessments prior to initial dosing, after the stable dialysis regimen is established. Post-treatment AUC measurements will be obtained at the Month 3 and Month 6 plasma oxalate profile assessments.

Long-term treatment effect of lumasiran will be summarized descriptively for the long-term extension period. Safety data will be summarized descriptively and presented in by-patient listings. Further details will be included in the SAP.

7.2.5.3. Exploratory Endpoints

Details will be included in the SAP.

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 primary 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 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 (and 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 (and assent form, if applicable). A copy of the signed ICF (and 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 patient consent form, 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 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).

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10. APPENDICES

10.1. Formulae for Estimated Glomerular Filtration Rate Calculation

Estimated glomerular filtration rate (eGFR; in mL/min/1.73 m^2) will be calculated from serum creatinine (SCr) based on the Schwartz Bedside Formula for patients ≥12 months to <18 years of age, and the Modification of Diet in Renal Disease Formula for patients ≥18 years of age.

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)

Modification of Diet in Renal Disease Formula[Levey 2009]

- Conventional units
  - eGFR (mL/min/1.73m^2) = 175 × (S_{Cr} [mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female), or × (1.212, if African American)
- SI units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [µmol/L]/88.4)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742, if female), or × (1.212, if African American)

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 15, which was adapted from the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document.

Table 15: 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	84-100	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-GO1-005 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 06 MAY 2020

ILLUMINATE-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1)

1. RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter dated 07 April 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]

This protocol amendment also incorporates the following 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, reduce patient burden regarding blood sampling, and clarify a study procedure pertaining to urine collection. These changes are summarized in Section 1.2 in Table 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 protocol changes is provided in Section 2 (Table 1). These measures were to be adopted immediately by the Investigator site as specified in the Dear Investigator Letter.

- **Screening period (notification of new patients)**

  The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given COVID-19 limitations.

- **Screening period and plasma oxalate eligibility (expanded windows)**

  To ensure adequate time to complete screening assessments, the screening window will be expanded from 60 days to 120 days; screening assessments previously obtained within 120 days prior to Day 1 may be used. However, echocardiogram and ECG will be repeated if obtained 60 or more days prior to Day 1, and 1 additional plasma oxalate will be performed if all 3 plasma oxalate assessments were obtained 60 or more days prior to Day 1. The plasma oxalate repeat collection should occur at least 7 days before Day 1.

  The three most recent screening plasma oxalate samples collected prior to Day 1, which may include the pre-dialysis sample from the plasma oxalate profile collection for Cohort B patients, will be used to assess eligibility.

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

  Following appropriate training and after consultation with the Medical Monitor, dosing will be permitted at a location other than the study center (eg, home), by the patient or patient's caregiver with the oversight of the Investigator, provided the patient has tolerated at least 1 dose of lumasiran administered in the clinic. 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.

- **Study visit window**

  Except for assessments with other specified timing requirements (as noted below), study assessments and dosing are to be performed within a visit window of ±14 days (previously ±7 days) for all patients through Month 6, and for patients who weigh <10 kg from Month 7 through the end of study, and within a visit window of ±28 days (previously ±14 days) for patients who weigh ≥10 kg from Month 7 through end of study. Study drug doses must be administered at least 21 days apart.

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

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

- **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.

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

  If the current procedure (weight obtained within 7 days or within 3 months prior to monthly or quarterly dose, respectively) is not possible due to the COVID-19 pandemic impacting activities at the study site or patient ability to access the site, dose will be based on weight obtained within 6 weeks prior to dosing for patients who are <10 kg and within 4 months for patients who are ≥10 kg.

  For Cohort B patients, if a post dialysis weight taken at the study center is not available within the above specified timeframes, weight taken at the dialysis center may be used.

- **24-hour urine sample collection**

  To avoid risks associated with use of urinary catheters and prolonged hospitalization, the option to use catheterization for 24-hour urine sample collection has been removed.

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

  The Vineland Behavior Scale, Quality of Life questionnaires, and Patient/Caregiver Experience and Impact questionnaires may be completed up to 4 months after the intended timepoint.

- **Systemic oxalosis assessments**

  Broader windows will be applied for systemic oxalosis assessments:

  - 12-lead ECGs may be completed up to 2 months after the Month 3 timepoint, 5 months after Month 6, and 11 months after Month 12
  - Renal ultrasounds may be completed up to 1 month after Day 1, 5 months after Month 6, and 11 months after Month 12
  - Echocardiogram may be completed up to 5 months after Month 6, and up to 11 months after Month 12
  - Radiographs, ophthalmology evaluation, and optional bone scan may be completed up to 1 month after Day 1 and up to 11 months after the Month 12 timepoint

- **Plasma oxalate profile**

  Plasma oxalate profile samples can be collected up to 2 months after the Month 3 timepoint, up to 5 months after the Month 6 timepoint, and up to 11 months after the Month 12 timepoint.

  If a patient's stable dialysis regimen at the time of consent is interrupted during screening for ≤14 days, plasma oxalate levels should not be collected until the prior dialysis regimen has resumed for at least 2 weeks.

If a patient's stable dialysis regimen at the time of consent is interrupted for >14 days, plasma oxalate should not be collected until the stable dialysis regimen has resumed for at least 4 weeks.

If a patient's stable dialysis regimen at the time of consent is permanently changed during screening, plasma oxalate should not be collected until the new dialysis regimen has been established for at least 4 weeks. Any plasma oxalate profiles and pre-dialysis plasma oxalate samples collected prior to this point will not be used for the study. A total of 2 plasma oxalate profiles and a pre-dialysis plasma oxalate sample need to be collected AFTER the new stable dialysis regimen has been established for at least 4 weeks.

The sampling times for plasma oxalate profile samples in protocol Table 6 are listed relative to dosing. If plasma oxalate profile samples are taken on a non-dosing day, these times (2:00, 4:00, 8:00, 12:00 and 24:00 hours post-dose) should correspond to the end of dialysis.

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

  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 including blood and urine collection, vital signs, weight, administration of study drug, an abbreviated physical examination/body system assessment, and a height/length measurement .

- **Pregnancy tests**

  Given the expanded use of offsite dosing, pregnancy tests will be permitted at an offsite location (eg, home) by a healthcare professional or the patient/patient's caregiver at all timepoints as of Month 1.

- **Pharmacokinetic assessments**

  In situations where the full PK profile (2, 4, 8, 12, and 24 hours post-dose plasma PK samples) cannot be drawn on the Day 1 visit, PK samples should be collected at 2, 4, and 24 hours. The next full PK profile will be drawn at Month 6 with a window of ±3 months.

- **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

Additional changes to study conduct (outlined below) will not be implemented until appropriate HA and EC/IRB approval. The removal of the requirement to perform routine 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.

- Remove the collection of blood samples to assess pyridoxine (Vitamin B6) levels after Month 12 and after discontinuation of pyridoxine therapy. After a patient discontinues pyridoxine therapy, measurement of pyridoxine is no longer medically indicated to verify medication compliance.
- Increase sample size based on feasibility; additional patients were identified since original protocol was implemented.
- Revise renal ultrasound and urine collection assessments as anephric patients are exempt from renal ultrasound and procedures requiring urine samples, and anuric patients are exempt from procedures requiring urine samples.
- Clarify ophthalmologic exams: Fundus photography (FP), Optical Coherence Test (OCT) and Fundus Autofluorescence (FAF) will be performed for all patients at specified timepoints; however, FAF will not be performed if unavailable at the study site.

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

2. PROTOCOL AMENDMENT 2 DETAILED SUMMARY OF CHANGES

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

The primary section(s) of the protocol affected by the changes in Protocol Amendment 1 are indicated. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: Ensure, to the extent possible, that study integrity is maintained.

The primary change occurs in Section 6.1, Screening Assessments

Added text:

The Investigator will notify the Sponsor before screening patients to allow an assessment of the ability of the site or any new trial participant to comply with the protocol given COVID-19 limitations.

Purpose: Expand the screening window and ensure adequate time to complete screening assessments.

The primary change occurs in Table 1 Schedule of Assessments Primary Analysis Period (Screening through Month 6): All Patients.

Revised text:

Study Period Study Visit		Screening
Study Day (±Visit Window)	Notes	~~-60~~ to -1 **-120** to -1

Section(s) also reflecting this change:

- Synopsis
- Synopsis Table 6, Pharmacokinetic and Plasma Oxalate Profile Assessment Time Points for Patients on Dialysis
- Section 3.1, Summary of Study Design
- Section 3.3, Duration of Study
- Section 6.1, Figure 1: Blood Sample Collection for PD Assessments During Screening
- Section 6.1.2, Rescreening
- Section 6.2.2 Urinary Oxalate, Table 12

Purpose: Expand the use of offsite administration to include lumasiran dosing by the patient or 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 patient or patient's 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 patient/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.

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

Section(s) also reflecting this change:

- Synopsis Tables 1, 2, 3, and 4, Schedules of Assessments

Purpose: Allow additional offsite assessments

The primary change occurs in Section 6, Study Assessments

Revised text: 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, **length/height** and weight, **an abbreviated physical examination/body system assessment**, and preparation and administration of study drug (at the discretion of the Investigator).

Section(s) also reflecting this change:

- Section 6.5.3, Physical Examination

- Section 6.5.5.2, Pregnancy Testing

Purpose: Remove optional catheterization to avoid risks associated with use of urinary catheters and prolonged hospitalization.

The primary change occurs in Section 3.1, Summary of Study Design

Revised text: 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 dose. There will be a single 24-hour urine collection at Month 3, Month 12, and every 6 months thereafter while on study. ~~For patients unable to provide 24-hour urine samples, a single catheterized 24-hour collection may be obtained, when allowed, at both baseline and Month 6. Catheterized collections may be performed at the discretion of the Investigator and with legal guardian assent or consent, and per local IRB/IEC approval.~~

Section(s) also reflecting this change:

- Section 6.2.2, Urinary Oxalate
- Section 6.2.2.1, Validity Criteria for 24-hour Urine Collection

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Purpose: 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: Liver function test (LFT) results (see Table 13) 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 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.**

Section(s) also reflecting this change:

- Section 5.2.2, Dose and Administration
- Section 6.5.5.3, Additional Liver Function Assessments

Purpose: Allow flexibility for plasma oxalate assessments.

The primary change occurs in Section 6.1, Screening Assessments

Revised text: The timing of samples collected during Screening for plasma oxalate and plasma glycolate will be as shown in Figure 1. ~~The four plasma oxalate assessments used to establish the baseline should be assessed over the span of at least 28 days and should be measured at least 7 days apart. The results of the first 3 baseline assessments will be used to determine eligibility. For patients in~~

~~Cohort B, 2 of the 4 baseline plasma oxalate assessments will be the pre-dialysis sample drawn at the beginning of the plasma oxalate profile.~~

The three most recent screening plasma oxalate samples collected prior to Day 1, which may include the pre-dialysis sample from the plasma oxalate profile collection for Cohort B patients, will be used to assess eligibility. If all 3 plasma oxalate assessments are obtained >60 days prior to Day 1, one additional plasma oxalate will be performed (at least 7 days prior to Day 1).

For subjects in Cohort B, there must be 2 separate plasma oxalate profile assessments performed during Screening, performed at least 1 week apart.

If a patient's stable dialysis regimen at the time of consent is interrupted during screening for ≤14 days, plasma oxalate levels should not be collected until the prior dialysis regimen has resumed for at least 2 weeks. If a patient's stable dialysis regimen at the time of consent is interrupted for >14 days, plasma oxalate should not be collected until the stable dialysis regimen has resumed for at least 4 weeks.

If a patient's stable dialysis regimen at the time of consent is permanently changed during screening, plasma oxalate should not be collected until the new dialysis regimen has been established for at least 4 weeks. Any plasma oxalate profiles and pre-dialysis plasma oxalate samples collected prior to this point will not be used for the study. A total of 2 plasma oxalate profiles and a pre-dialysis plasma oxalate sample need to be collected AFTER the new stable dialysis regimen has been established for at least 4 weeks.

Section(s) also reflecting this change:

- Synopsis Table 6, Pharmacokinetic and Plasma Oxalate Profile Assessment Time Points for Patients on Dialysis
- Section 6.2.1.1, Cohort A
- Section 6.2.1.2, Cohort B

Purpose: Expand windows for measures of systemic oxalosis

The primary change occurs in Section 6.2.3, Measures of Systemic Oxalosis

Revised text: Triplicate 12-lead ECGs will be collected using standardized machines 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 2 months after the Month 3 timepoint, up to 5 months after the Month 6 timepoint, and up to 11 months after the Month 12 timepoint.** 12-lead ECGs will be centrally read.

Radiographs (X-rays**)** of hands, hip, knee, and chest will be obtained and read centrally for features of skeletal oxalosis, where local IRB/IEC permits at the timepoints specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4), where feasible based on patient compliance. **During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, X-rays may be completed up to 1 month after Day 1, and up to 11 months after the Month 12 timepoint.**

Optional bone scans will be performed in only Cohort B patients ≥18 years of age to assess calcium oxalate systemic deposition, where local IRB/EC permits and if patient consents to the bone scan. **During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, optional bone scans may be completed up to 1 month after Day 1, and up to 11 months after the Month 12 timepoint**.

Section(s) also reflecting this change:

- Section 6.2.3.1, Cardiac
- Section 6.2.3.3, Skeletal
- Section 6.2.3.4, Ocular

Purpose: Expand windows for Quality of Life assessments

The primary change occurs in Section 6.7, Developmental Assessments

Revised text: 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 by a legal guardian or caregiver in approximately 20 to 60 minutes.

Section(s) also reflecting this change:

- Section 6.8, Quality of Life Questionnaires
- Section 6.9, Patient/Caregiver Experience Surveys and Impact Questionnaires

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

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

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.**

Section(s) also reflecting this change:

- Section 4.3.3, Lost to Follow-up

Purpose: To expand study window for assessment of weight prior to dosing.

The primary change occurs in Section 5.2.2, Dose and Administration

Revised text: **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 dose will be based on weight obtained within **6 weeks** prior to dosing for patients who are ~~<6 years of age~~**<10 kg** and within **4 months** for patients ~~≥6 years of age~~ **who weigh ≥10 kg**. **For Cohort B patients, if a post dialysis weight taken at the study center is not available within the specified timepoints, post dialysis weight taken at the dialysis center may be used**.

Purpose: To adjust the plasma oxalate sampling times to accommodate profile samples taken on non-dosing days to ensure patient safety and, to the extent possible, that study integrity is maintained amid travel and other restrictions related to the COVID-19 pandemic.

The primary change occurs in Table 6, Pharmacokinetic and Plasma Oxalate Profile Assessment Time Points for Patients on Dialysis

Added text: **The plasma oxalate profile can be obtained on non-dosing days and the 2:00, 4:00, 8:00, 12:00, and 24:00 timepoints will be post dialysis.**

Section(s) also reflecting this change:

- Section 6.2.1, Plasma Oxalate

Purpose: Reduce required collection timepoints for PK assessments to limit the potential exposure of the patient to COVID-19.

The primary change occurs in Table 5, Pharmacokinetic Time Points: All Patients

Added text: Day 1 and Month 6 **(±3 mos)**

- **Blood samples for PK assessment may be collected at 8 and 12 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.**

Purpose: Added collection of information related to the impact of the COVID-19 pandemic on patient participation in the study for each patient to enable an evaluation of the impact of the COVID-19 global pandemic on clinical study data.

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: To provide clarification on Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

The primary changes occur in Section 8.1.1, Informed Consent and Section 8.1.2, Ethical Review

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.

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.

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: To increase sample size

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

Revised text:

The planned enrollment for this study is ~~16~~ **20** patients, including 6 patients in each cohort.

Section(s) also reflecting this change:

- Synopsis
- Section 7.1, Determination of Sample Size

Purpose: To remove the requirement for measurement of routine coagulation

The primary change occurs in Section 6.5.5, Clinical Laboratory Assessments: Table 13, Clinical Laboratory Assessments;

Revised text:

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

Section(s) also reflecting this change:

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

Purpose: Remove the requirement for measurement of pyridoxine after Month 12.

The primary change occurs in Table 2 Schedule of Assessments – Long-term Extension Period (Month 7 to Month 35): Patient Weight <10 kg; and Table 4, Schedule of Assessments – Long-term Extension Period (Month 9 to End of Study): Patient Weight ≥10 kg

Deleted text: Deleted X in schedule of assessment table cells for timepoints after Month 12.

Sections also reflecting this change:

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

- Table 13, Clinical Laboratory Assessments

Purpose: To clarify renal ultrasound and urine collection assessments as anephric patients are exempt from renal ultrasound and procedures requiring urine samples, and anuric patients are exempt from procedures requiring urine samples.

The primary change occurs in Section 6.3.1, Renal Ultrasound

Added text: Renal ultrasounds will be obtained locally, as specified in the Schedules of Assessment (see Table 1, Table 2, Table 3, and Table 4) **when feasible; anephric patients are exempt from renal ultrasound assessments.** Renal ultrasound will be performed according to instructions provided in the Study Manual in a standardized manner. Renal ultrasounds will be reviewed centrally.

Section(s) also reflecting this change:

- Section 6, Study Assessments

Purpose: To clarify Fundus Autofluorescence (FAF) will be performed for all patients at specified timepoints; however, FAF needs to be performed only at select sites where the procedure is available.

The primary change occurs in Section 6.2.3.4, Ocular

Revised text: The following ophthalmologic exams will be performed: Color Fundus Photography (CFP), Optical Coherence Tomography (OCT), and, where available at select sites, Fundus Autofluorescence (FAF). ~~along with color fundus photography (where available at select sites), and retinal Optical Coherence Tomography (OCT) with autofluorescence.~~

Ophthalmologic exams with fundus photography will be standardized and the fundus photographs will be read centrally. OCT assessments will also be standardized and read centrally. For young children unable to cooperate, examinations will be optional. Anesthesia will not be used in any of these ocular assessments. Results from any clinically obtained exams performed as standard of care may be collected.

Best Corrected Visual Acuity (BCVA)

Where available, BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts will be assessed longitudinally throughout the course of the study to evaluate for changes which correspond to changes in retinal oxalate deposition. Exams will be standardized across **applicable** sites. In younger patients <6 years of age, alternate visual acuity testing per local standard practice may be performed (eg, LEA symbols). **In sites where ETDRS testing is not available, Snellen or LEA symbol charts may be used for BCVA**. Testing is not required in preverbal infants.

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