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

NCT Number: **NCT03681184**

Document Date: **Protocol Amendment 2, 19 March 2019**

CLINICAL STUDY PROTOCOL

ALN-GO1-003

Protocol Title:	ILLUMINATE-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1
Short Title:	A Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2018-001981-40
IND Number:	128941
Sponsor:	Original protocol, 09 July 2018 Amendment 1, 23 July 2018 Amendment 2, 19 March 2019
Sponsor Contact:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200 [redacted] MD [redacted]

SPONSOR PROTOCOL APPROVAL

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

[redacted]

20 Mar 2019

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-003 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to ensure that Financial Disclosure Statements will be completed by me (including, if applicable, my spouse [or legal partner] and dependent children), my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status. 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-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Short Title

A Phase 3 Study to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Study Drug

Lumasiran (ALN-GO1)

Phase

Phase 3

Study Center(s)

The study will be conducted at approximately 20 clinical study centers worldwide.

Objectives and Endpoints

Primary	
• To evaluate the effect of lumasiran on percent reduction in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate excretion from baseline to Month 6
Secondary	
• To characterize the effect of lumasiran on absolute levels of urinary oxalate excretion, oxalate:creatinine ratios, and plasma oxalate • To evaluate the effect of lumasiran, on renal function • To evaluate the long-term treatment effect of lumasiran	• Absolute change in 24-hour urinary oxalate corrected for body surface area (BSA) from baseline to Month 6 • Change in 24-hour urinary oxalate:creatinine ratio (value/upper limit of normal [ULN]) from baseline to Month 6 • Proportion of patients with 24-hour urinary oxalate level at or below 1.5 x ULN at Month 6 • Proportion of patients with 24-hour urinary oxalate level at or below ULN at Month 6 • Percent change in plasma oxalate from baseline to Month 6 • Absolute change in plasma oxalate from baseline to Month 6

	• Change in estimated glomerular filtration rate (eGFR) from baseline to Month 6 • Change from baseline (percent and absolute) in 24-hour urinary oxalate excretion, percentage of time that 24-hour urinary oxalate is ≤1.5 × ULN, 24-hour urinary oxalate:creatinine ratios and eGFR in the extension periods
Exploratory	
• To evaluate quality of life (QoL) • To evaluate the change in nephrocalcinosis and renal stones • To evaluate the additional pharmacodynamic (PD) parameters of plasma glycolate, urinary glycolate, and urinary oxalate in spot urine collections • To characterize the pharmacokinetics (PK) of lumasiran • To assess for antidrug antibodies (ADA) against lumasiran • To evaluate the effects of lumasiran on patient and caregiver resource use • To describe the patient experiences on lumasiran in PH1 patients and the experiences of caregivers for these patients	• Change in Kidney Disease Quality of Life Questionnaire (KDQOL) for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL [the generic and end-stage renal disease (ESRD) modules]) for patients <18 years of age at screening • Change in Euro Quality of Life Health State Profile Questionnaire (EQ-5D) and EQ-5D Visual Analog Scale (VAS) • Change in rate of renal stone events • Change in nephrocalcinosis as assessed by renal ultrasound • Change in urinary and plasma glycolate • Change in urinary oxalate:creatinine ratios as assessed in random spot urine collections • PK profile of lumasiran • Frequency of ADA • Change in patient resource use (eg, work/school attendance, visits to doctor/hospital) • Change in patient and caregiver experiences as evaluated by patient and caregiver experience surveys
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency and seriousness of adverse events (AEs) during the 6-month double-blind treatment period and in the extension periods

Study Design

This is a multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of lumasiran in patients with PH1 ≥ 6 years of age with relatively preserved renal function. The study will

be conducted in 3 parts: a 6-month, placebo-controlled, double-blind treatment period followed by a 3-month blinded treatment extension period and an open-label extension period of up to 51 months. A schematic of the study design is shown in Figure 1.

Number of Planned Patients
The planned enrollment for this study is 30 patients.

Diagnosis and Main Eligibility Criteria
This study will include adults and children (≥6 years of age) with a documented diagnosis of PH1 based on urinary oxalate excretion ≥0.70 mmol/24h/1.73m^2 and confirmed alanine glyoxylate aminotransferase (*AGXT*) mutations, and eGFR ≥30 mL/min/1.73m^2 at screening.

Study Drug, Dose, and Mode of Administration
Lumasiran (ALN-GO1) 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.

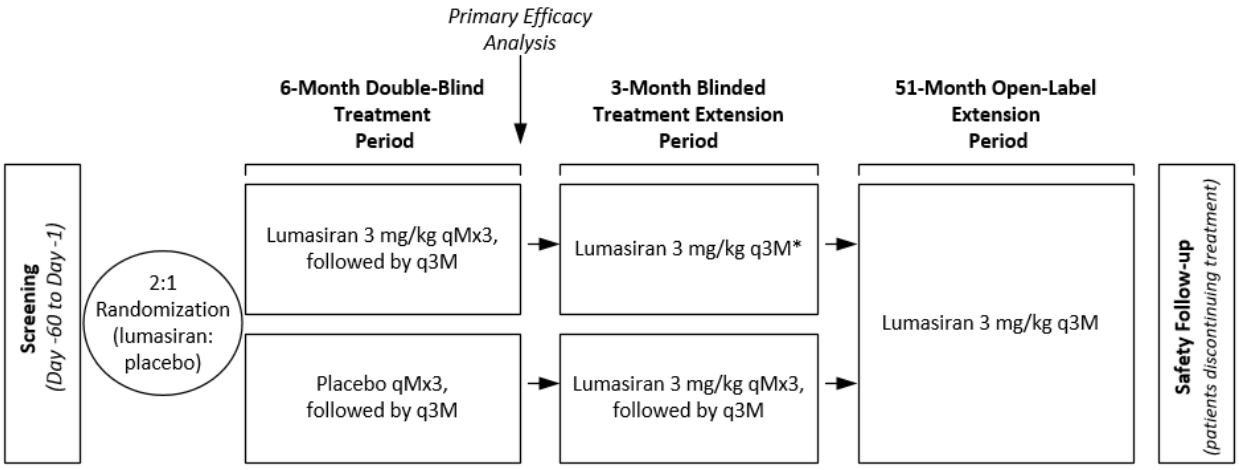
Lumasiran will be administered at a dose of 3.0 mg/kg as a subcutaneous (SC) injection. See Figure 1 for the dose schedule.

Reference Treatment, Dose, and Mode of Administration
The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). See Figure 1 for the dose schedule.

Duration of Treatment and Study
The duration of treatment with study drug is up to 5 years, including a 6-month double-blind treatment period followed by a 3-month blinded treatment extension period, and up to a 51-month open-label extension period.

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

Figure 1: Study Design



Abbreviations: q3M=once every 3 months; qM=once monthly; qMx3=once monthly for 3 consecutive months
* Patients randomized to lumasiran will also receive 2 qM doses of placebo during the 3-month blinded treatment extension period.

Table 1: Schedule of Assessments – 6-Month Double-Blind Treatment Period and Blinded Treatment Extension (Screening through Month 9 Assessments)

		Screening	6-Month Double-Blind Treatment Period								3-Month Blinded Treatment Extension Period		
Study Visit			**Base line**	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
Study Day (±Visit Window)	**Note**	**-60 to -1**	**Day 1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**	**197 (±4)**	**225 (±4)**	**253 (±4)**
Informed consent (and assent, if applicable)	If during the study the patient reaches the legal age for consent, the patient needs to consent before any study procedures can be performed	X											
Demographics		X											
Medical history	See Section 6.1.	X	X										
Inclusion/exclusion criteria		X											
Randomization	May be done 1 business day prior to Day 1 for study drug preparation.		X										
Full physical examination	See Section 6.5.3.	X								X			
Symptom-directed physical examination	See Section 6.5.3.		X	X	X	X	X	X	X		X	X	X
Height	In triplicate for pediatric patients. See Section 6.5.2.	X	X							X			
Body weight	See Section 6.5.2.	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	See Section 6.5.1. On Day 1 and Month 6 only, to be measured predose and 30±10minutes postdose	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	See Section 6.5.4 and Table 3. For East Asian sites, see Table 4.	X	X				X			X			X

		Screening	6-Month Double-Blind Treatment Period								3-Month Blinded Treatment Extension Period		
Study Visit			**Base line**	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
Study Day (±Visit Window)	**Note**	**-60 to -1**	**Day 1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**	**197 (±4)**	**225 (±4)**	**253 (±4)**
Follicle-stimulating hormone	Only if applicable to confirm postmenopausal status.	X											
Serum pregnancy test (for WOCBP)	See Section 6.5.6.2. Performed after the onset of menarche, if applicable.	X											
Urine pregnancy test (for WOCBP)	May be performed more frequently where required per local requirements, or if pregnancy is suspected. See Section 6.5.6.2.		X		X	X	X			X	X	X	X
DNA sample for PH1/*AGXT* mutation analysis	Only for patients without documented PH1 genetic analysis.	X											
Exploratory DNA sample (optional)	See Section 6.6.		X										
Clinical laboratory assessments	See Section 6.5.6.	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration	Dosage is based on total body weight. On M6, all assessments, except PK, should be completed prior to dosing. Quality of life and patient experience and resource-use instruments can be completed after the dose is administered. See Section 5.2.2.		X		X	X	X			X	X	X	X
Blood samples for PK analyses	See Table 3. For East Asian sites, see Table 4.		X				X			X			X
Urine samples for PK analyses	Patients at East Asian sites only; see Table 5.		X							X			

		Screening	6-Month Double-Blind Treatment Period								3-Month Blinded Treatment Extension Period		
Study Visit			**Base line**	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
Study Day (±Visit Window)	**Note**	**-60 to -1**	**Day 1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**	**197 (±4)**	**225 (±4)**	**253 (±4)**
Blood sample for PD analyses		X	X		X	X	X	X	X	X	X	X	X
≥3 separate 24-hour urine collection for PD analyses	≥2 collections must be valid. At M6, collect within 14 days prior to dosing. See Section 6.3.1 and Table 7.	X								X			
Single 24-hour urine collection for PD analyses	Collect within 7 days prior to dosing (M1, M2, M3, M7, M8, M9) or visit (M4, M5). If invalid, should be repeated. See Section 6.3.1 and Table 7.				X	X	X	X	X		X	X	X
Random urine sample for PD analysis	See Section 6.3.1 and Section 6.3.1.2 .	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for pyridoxine (vitamin B6) levels	Only if taking pyridoxine for the treatment of PH1. To be collected ≥6 hours from last dose of pyridoxine. See Section 5.3.	X	X		X	X	X	X	X	X	X	X	X
Renal stone events	See Section 6.3.3.	Continuous											
Renal ultrasound	Analyzed centrally by blinded reader. See Section 6.5.5.	X								X			
Quality of life questionnaires	See Section 6.7.	X								X			
Patient and caregiver experience surveys	See Section 6.8.	X								X			
Patient and caregiver impact questionnaire	See Section 6.9.	X								X			

		Screening	6-Month Double-Blind Treatment Period								3-Month Blinded Treatment Extension Period		
Study Visit			**Base line**	**Wk 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
Study Day (±Visit Window)	**Note**	**-60 to -1**	**Day 1**	**15 (±3)**	**29 (±4)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±7)**	**197 (±4)**	**225 (±4)**	**253 (±4)**
Healthcare resource utilization	See Section 6.10.	Continuous											
Antidrug antibody sample	See Section 6.5.6.1.		X		X		X			X	X		X
Blood and urine samples for exploratory analyses	See Section 6.6.	X	X		X		X			X			X
Review/record adverse events	SAEs (only) are collected in the Screening period. Starting on Day 1, all AEs (ie, including SAEs) are collected. See Section 6.5.7.2.	Continuous											
Prior and concomitant medications	See Section 5.3.	Continuous											

Abbreviations: AE=adverse event; *AGXT*=alanine glyoxylate aminotransferase (gene); DNA=deoxyribonucleic acid; ECG=electrocardiogram; M=month; PD=pharmacodynamic; PH1=primary hyperoxaluria type 1; PK=pharmacokinetic; SAE=serious adverse event; Wk=week; WOCBP=women of child-bearing potential

Notes:

- Assessments to be performed prior to dosing, where applicable. Pregnancy test results must be known prior to dosing, if applicable. Where feasible, when scheduled at the same time points, the assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations, and blood sample collections.
- Gray-shaded column indicate visits where assessments span 2 days.
- See Section 4.3.1 for instructions for patients who discontinue study drug.

Table 2: Schedule of Assessments – Open Label Extension Period (After Month 9 through Year 5)

Study Period		Open-Label Extension Period									Safety Follow-up (Patients who Discontinue Treatment)
		Through Year 2						Through Year 5			
Study Visit		**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30; M36; M42; M48; M54**	**EOT M57**	**EOS/ ET M60**	
Study Day (±Visit Window)	**Note**	**337 (±7)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**Every 168 days (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Informed consent (and assent, if applicable)	If during the study the patient reaches the legal age for consent, the patient needs to consent before any study procedures can be performed										
Full physical examination	See Section 6.5.3.	X		X		X		X		X	
Symptom-directed physical examination	See Section 6.5.3.		X		X						X
Height	In triplicate for pediatric patients. See Section 6.5.2.	X		X		X		X		X	X
Body weight	See Section 6.5.2.	X	X	X	X	X		X		X	X
Vital signs	See Section 6.5.1.	X	X	X	X	X		X		X	X
12-lead electrocardiogram	See Section 6.5.4 and Table 3. For East Asian sites, see Table 4.	X				X		X (M36 and M48 only)		X	
Pregnancy test (WOCBP)	May be performed more frequently where required per local requirements, or if pregnancy is suspected. See Section 6.5.6.2.	X	X	X	X	X	X	X (every 84 days predose)	X	X	X
Clinical laboratory assessments	See Section 6.5.6.	X	X	X	X	X		X		X	X

Study Period		**Open-Label Extension Period**									**Safety Follow-up** (Patients who Discontinue Treatment)
		Through Year 2						**Through Year 5**			
Study Visit		**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30; M36; M42; M48; M54**	**EOT M57**	**EOS/ ET M60**	
Study Day (±Visit Window)	**Note**	**337 (±7)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**Every 168 days (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Study drug administration	Study drug to be administered every 3 months through M57. Dosage is based on total body weight. See Section 5.2.2.	X	X	X	X	X	X	X (every 84 [±14] days)	X		
Blood samples for PK analyses	See Table 3. For East Asian sites, see Table 4.	X									
Urine samples for PK analyses	Patients at East Asian sites only; see Table 5.	X									
Blood sample for PD analyses		X	X	X	X	X		X		X	X
≥3 separate 24-hour urine collection for PD analyses	≥2 collections must be valid. Collect within 14 days prior to dosing. See Section 6.3.1 and Table 7 for details.	X									
Single 24-hour urine collection for PD analyses	Collect within 14 days prior to dosing or visit. If invalid, should be repeated. See Section 6.3.1 and Table 7.		X	X	X	X		X		X	X
Random urine sample for PD analysis	See Section 6.3.1 and Section 6.3.1.2.	X	X	X	X	X		X		X	X
Blood sample for pyridoxine (vitamin B6) levels	Only if taking pyridoxine for the treatment of PH1. To be collected ≥6 hours from last dose of pyridoxine. See Section 5.3.	X	X	X	X	X		X		X	
Renal stone events	See Section 6.3.3.	Continuous									

Study Period		**Open-Label Extension Period**									**Safety Follow-up** (Patients who Discontinue Treatment)
		Through Year 2						**Through Year 5**			
Study Visit		**M12**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30; M36; M42; M48; M54**	**EOT M57**	**EOS/ ET M60**	
Study Day (±Visit Window)	**Note**	**337 (±7)**	**421 (±14)**	**505 (±14)**	**589 (±14)**	**673 (±14)**	**757 (±14)**	**Every 168 days (±14)**	**1597 (±14)**	**1681 (±14)**	**Every 84 days (±14)**
Renal ultrasound	See Section 6.5.5.	X				X		X (M36 and M48 only)		X	
Quality of life questionnaires	See Section 6.7.	X		X		X		X		X	
Patient and caregiver experience surveys	See Section 6.8.	X		X		X		X		X	
Patient and caregiver impact questionnaire	See Section 6.9.	X		X		X		X		X	
Healthcare resource utilization	See Section 6.10.	Continuous									
Antidrug antibody sample		X		X		X		X		X	X
Blood and urine samples for exploratory analyses	See Section 6.6.	X		X		X		X		X	
Review/record adverse events	See Section 6.5.7.2.	Continuous									
Prior and concomitant medications	See Section 5.3.	Continuous									

Abbreviations: ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; M=month; PD=pharmacodynamic; PH1=primary hyperoxaluria type I; PK=pharmacokinetic; WOCBP=women of child-bearing potential

Notes:
- Assessments are to be performed prior to dosing, where applicable. When applicable, pregnancy test results must be known prior to dosing. 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.
- Where applicable country and local regulations and infrastructure allow, lumasiran administration may take place at a location other than the study center by a home healthcare professional beginning at Month 15 (at the discretion of the Investigator, based on safety and tolerability). Study drug is administered once every 3 months throughout the open-label extension period.
- See Section 4.3.1 for instructions for patients who discontinue study drug.
- Gray-shaded column indicates the visit where assessments span 2 days.

Table 3: Pharmacokinetic and ECG Assessment Time Points: All Sites except East Asian Sites

Study Month/ Study Day	Sampling Time (hh:mm)	Blood PK Sample	ECG
Screening	Any time during visit		X[a]
Month 0 (Day 1)	Predose	X	X[b]
	04:00 (±1 hour)	X	X[b]
	24:00 (±2 hours)	X	
Month 3 (Day 85± 4 days)	Predose	X	X[a]
	04:00 (±1 hour)	X	
Month 6 (Day 169±7 days)	Predose	X	X[b]
	04:00 (±1 hour)	X	X[b]
	24:00 (±2 hours)	X	
Month 9 (Day 253±4 days)	Predose	X	X[a]
	04:00 (±1 hour)	X	
Month 12 (Day 337±7 days)	Predose	X	X[a]
	04:00 (±1 hour)	X	
	24:00 (±2 hours)	X	
Months 24, 36, 48, 60 (see Table 2)	Predose		X[a]

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

Notes:

- Predose samples are collected on the day of dosing.
- The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. See Section 7.2.7 for additional information on PK assessments.
- Patients should be supine for at least 10 minutes before each ECG is obtained. See Section 6.5.4 for additional information on ECG assessments.

[a] For Screening, Month 3, Month 9, Month 12 and annual visits (Month 24, Month 36, Month 48, Month 60), singlicate ECGs are performed using a local ECG machine.

[b] For Month 0 (Day 1) and Month 6, triplicate ECGs are performed predose and postdose timepoints using a central machine and central reads. Triplicate ECG readings occur approximately 5 minutes apart.

Table 4: Pharmacokinetic and Electrocardiogram Assessment Time Points: East Asian Sites

Study Month (Study Day)	**Sampling Time (hh:mm)**	**Blood PK Sample**	**ECG**
Screening	Any time during visit		X[a]
Month 0 (Day 1)	Predose	X	X[b]
	00:30 (±10 min)	X	
	02:00 (±20 min)	X	
	04:00 (±20 min)	X	X[b]
	06:00 (±20 min)	X	
	08:00 (±20 min)	X	
	24:00 (±2 hours)	X	X[b]
Month 3 (Day 85±4 days)	Predose	X	X[a]
	04:00 (±1 hour)	X	
Month 6 (Day 169±7 days)	Predose	X	X[b]
	00:30 (±10 min)	X	
	02:00 (±20 min)	X	
	04:00 (±20 min)	X	X[b]
	06:00 (±20 min)	X	
	08:00 (±20 min)	X	
	24:00 (±2 hours)	X	X[b]
Month 9 (Day 253±4 days)	Predose	X	X[a]
	04:00 (±1 hour)	X	

Study Month (Study Day)	**Sampling Time (hh:mm)**	**Blood PK Sample**	**ECG**
Month 12 (Day 337±7 days)	Predose	X	X[b]
	00:30 (±10 min)	X	
	02:00 (±20 min)	X	
	04:00 (±1 hour)	X	X[b]
	06:00 (±20 min)	X	
	08:00 (±20 min)	X	
	24:00 (±2 hours)	X	X[b]
Months 24, 36, 48, 60 (see Table 2)	Predose		X[a]

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

Notes:

- East Asian includes sites in China, Korea, Japan, Taiwan, and Hong Kong.
- Predose samples are collected on the day of dosing.
- The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. See Section 7.2.7 for additional information on PK assessments.
- Patients should be supine for at least 10 minutes before each ECG is obtained. See Section 6.5.4 for additional information on ECG assessments.

[a] For Screening, Month 3, Month 9, and annual visits (Month 24, Month 36, Month 48, Month 60), singlicate ECGs are performed using a local ECG machine.

[b] For Month 0 (Day 1), Month 6, and Month 12 triplicate ECGs are performed predose and postdose timepoints using a central machine and central reads. Triplicate ECG readings occur approximately 5 minutes apart.

Table 5: Urine Pharmacokinetic Assessment Time Points: East Asian Sites

Study Day	Sampling Time (hh:mm)	Pooled Urine PK Sample
Month 0 (Day 1)	Predose	X
	0-6 hours (±30 min)	X
	6-12 hours (±30 min)	X
	12-24 hours (±2 hours)	X
Month 6 (Day 169 ±7 days)	Predose	X
	0-6 hours (±30 min)	X
	6-12 hours (±30 min)	X
	12-24 hours (±2 hours)	X
Month 12 (Day 337±7 days)	Predose	X
	0-6 hours (±30 min)	X
	6-12 hours (±30 min)	X
	12-24 hours (±2 hours)	X

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

- East Asian includes sites in China, Korea, Japan, Taiwan, and Hong Kong.
- The hour (±range) indicate sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. See Section 6.4.1 and Section 7.2.7 for additional information on PK assessments.
- All predose samples are spot urine samples; postdose urine samples are pooled samples.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AGT	Alanine-glyoxylate aminotransferase
AGXT	Alanine glyoxylate aminotransferase gene
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
BSA	Body surface area
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulation
CL/F	Apparent clearance
DMC	Data Monitoring Committee
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
FAS	Full analysis set
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GO	Glycolate oxidase
HAO1	Hydroxyacid oxidase 1
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRS	Interactive Response System
ISR	Injection site reactions
KDQOL	Kidney Disease Quality of Life Questionnaire
LFT	Liver function tests
MAD	Multiple-ascending dose
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MNAR	Missing not at random
mRNA	Messenger ribonucleic acid
OLE	Open-label extension
PD	Pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PH1	Primary hyperoxaluria type 1
PK	Pharmacokinetic
PMM	Pattern mixture model
PP	Per protocol
PT	Preferred Term
q3M	Once every 3 months
qM	Once monthly
qMx3	Once monthly for 3 consecutive months
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
siRNA	Small interfering RNA
SOC	System Organ Class

Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse reaction
$t_{½\beta}$	Elimination half-life
t_{max}	Time to maximum plasma concentration
TMF	Trial master file
ULN	Upper limit of normal
V/F	Apparent volume of distribution
VAS	Visual analog scale
WOCBP	Women of child-bearing potential
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.[1] 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.[1] 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.[1] Without treatment, the disease progresses inexorably, and death from end-stage renal disease (ESRD) and/or complications of oxalosis is inevitable.[1-3]

Over 150 mutations in *AGXT* have been described.[4] 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.[5, 6] 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.[1, 7, 8] The disease is more prevalent in areas where consanguineous marriages are common, especially in the Middle East and Northern Africa.[9-12]

PH1 often presents as a pediatric disease, but many patients remain undiagnosed for years after the initial clinical manifestations of the disease.[13-15] A recently published analysis of 247 patients with PH1 from 206 pedigrees in the Rare Kidney Stone Consortium PH Registry demonstrated a median age of first symptoms at 5.2 years of age and a cumulative renal survival of 76%, 43%, and 12% at 20 years, 40 years, and 60 years, respectively.[7] 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. Overall, 43% of all patients diagnosed with PH1 had already progressed to ESRD at the time of diagnosis.[14] The deterioration of renal function highlights the importance of investigating potentially disease-modifying interventions as soon as possible after diagnosis.

There are no approved therapies for the treatment of PH1 and the current standard of care is burdensome to patients and their families. Disease management is based on supportive measures, including high fluid intake and crystallization inhibitors to increase urinary oxalate solubility, and treatment of disease complications such as urinary tract stones and infections. A minority of patients experience oxalate lowering with therapeutic doses of pyridoxine (vitamin

B6). Dietary modification plays a minor role in treatment since endogenous oxalate production far exceeds dietary intake. Patients progressing to, or presenting with ESRD require intense kidney dialysis. Dialysis is not viewed as an effective therapy for PH1, but rather serves as a bridge to a liver-kidney transplant or as an alternative to no therapy at all. Dialysis is often inadequate to effectively offload accumulating oxalate, and systemic oxalosis with end organ damage may develop despite this burdensome treatment. Dialysis regimens for PH1 are more involved 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 [1], and intense use of health care resources.

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

1.2. Lumasiran (ALN-GO1)

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.

The proposed indication for lumasiran is the treatment of primary hyperoxaluria type 1 (PH1).

1.2.1. Summary of Nonclinical Data with Lumasiran

The pharmacology, safety pharmacology, pharmacokinetics, and toxicology of lumasiran were evaluated in a series of in vitro and in vivo nonclinical studies. Lumasiran was pharmacologically active in rodents and cynomolgus monkeys (hereafter referred to as monkeys). 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.

No lumasiran-related safety pharmacology findings were identified in Good Laboratory Practice (GLP)-compliant repeat dose toxicity studies in monkeys. Lumasiran was well tolerated in both the rat and monkey repeat dose toxicology studies and did not result in any dose-limiting effects at the highest doses tested. In vitro and in vivo genetic toxicity studies were all negative at (ICH) S2 (R1) limit doses. Based on this class of drugs and the data to date, a favorable safety profile of lumasiran has been demonstrated and supports the use of lumasiran in the current study.

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

1.2.2. Summary of Clinical Data with Lumasiran

Lumasiran is being investigated in 2 ongoing clinical studies, Study ALN-GO1-001 and Study ALN-GO1-002.

Study ALN-GO1-001 is a 2-part (single-ascending dose [SAD] and multiple-ascending dose [MAD]) study designed to evaluate the safety, tolerability, PK, and PD of lumasiran in healthy adult subjects and in adult and pediatric patients with PH1. In the SAD part of the study (Part A), healthy adult subjects were randomized to receive one single blind dose of lumasiran (0.3-6.0 mg/kg) or placebo (6:2). In the MAD part of the study (Part B), patients ≥6 years of age with PH1 and eGFR>45 mL/min/1.73 m^2 were randomized 3:1 to receive single blind doses of lumasiran or placebo at 1 mg/kg monthly for 3 doses, 3 mg/kg monthly for 3 doses or 3 mg/kg every 3 months for 2 doses. Patients who initially received placebo transitioned to an open-label portion of the study to receive doses of lumasiran. The primary objective is to evaluate the safety and tolerability of subcutaneously administered lumasiran. Secondary and exploratory objectives of the study include the characterization of plasma and urine PK and the evaluation of the PD effect, including glycolate and oxalate levels.

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

Available safety data indicate that lumasiran has an acceptable safety and tolerability profile across all dosing regimens evaluated. Preliminary data from Study ALN-GO1-001 demonstrate a mean maximal reduction in 24-hour urinary oxalate of 64% (Cohorts 1-3) and achievement of normal to near-normal levels of urinary oxalate (<0.70 mmol/24h/1.73 m^2) in patients dosed with lumasiran (range: 0.29 to 0.67 mmol/24h/1.73 m^2). Further information on the chemistry, pharmacology, efficacy, and safety of lumasiran is provided in the current edition of the Investigator's Brochure.

1.3. Study Design Rationale

Lumasiran is proposed to reduce urinary oxalate production resulting in lower urinary oxalate excretion in patients with relatively intact renal function. In preclinical models and in patients with PH1, SC administration of lumasiran demonstrated potent, dose-dependent pharmacologic activity resulting substantial reductions in urinary oxalate.[16]

This is a multicenter, multinational, randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the clinical efficacy and safety of lumasiran in patients with PH1. The primary endpoint for the study is percent change in 24-hour urinary oxalate excretion from baseline to Month 6.

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

The primary endpoint will evaluate the effect of lumasiran versus placebo on urinary oxalate at Month 6. After 6 months, patients originally assigned to lumasiran will continue to receive lumasiran, and patients originally assigned to placebo will receive lumasiran in a blinded extension period through Month 9 to preserve blinding. Patients randomized to lumasiran will receive injections of placebo at Month 7 and Month 8 to maintain the blind. All patients will then be followed in an open-label period of up to 51 months to evaluate the long-term safety and efficacy of lumasiran. Use of a placebo comparator and limiting the duration of placebo exposure to the 6-month double-blind period are appropriate based on the lack of approved therapies for patients with PH1 while allowing an estimation of the treatment effect and an understanding of the safety profile of lumasiran. All patients will continue their current standard of care regimen, which may include hyperhydration, crystallization inhibitors, and/or pyridoxine therapy, for the first 12 months of the study, after which they can adjust per the recommendations of their treating physician. Current disease management options are presented in Section 1.1.

The study population will be comprised of children and adults with a documented diagnosis of PH1, elevated urinary oxalate, and GFR ≥30 mL/min/1.73m^2. Lumasiran is currently being investigated in a similar patient population (ie, patients with PH1 ≥6 years of age with relatively intact renal function) in Study ALN-GO1-001. Enrolling pediatric patients in this study is acceptable given that PH1 presents as a pediatric disease with life-threatening consequences and hence there is a high unmet medical need in this population.

1.4. Dose Rationale

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 for this study. The proposed dosing regimen for this study is 3.0 mg/kg once monthly for 3 consecutive months (monthly for 3 doses: loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after the last loading dose. This regimen is expected to be well-tolerated and to optimize the proportion of patients with a rapid and sustained reduction in urinary oxalate.

In patients with PH1, 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 relationship. For a given dose, the PK/PD model indicated that monthly administration leads to a more rapid decline in urinary oxalate levels relative to dosing every 3 months. A combination of monthly dosing in a loading phase and then dosing every 3 months in a maintenance phase achieves the goals of rapid and consistent lowering of urinary oxalate to normal or near normal levels in PH1 patients. Preclinical and clinical data indicate the renal pathway is a minor elimination route for lumasiran. Thus, renal impairment is not expected to influence systemic exposure, PD, and safety properties of lumasiran, and no dose adjustments are needed based on renal function. Thus, a lumasiran dosing regimen of 3.0 mg/kg once monthly for 3 doses followed by 3.0 mg/kg once every 3 months has been selected for this study in PH1 patients ≥6 years old with eGFR ≥30 mL/min/1.73 m^2.

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, often progressing to end-stage renal disease. Systemic accumulation of calcium oxalate results in severe end-organ damage. Without treatment, the disease progresses, and patients die from end-stage renal disease and/or complication of oxalosis.

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

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

Given the biological target of lumasiran, the available nonclinical and clinical data, and mode of administration, important potential risks for lumasiran are injection site reactions and liver function test abnormalities. During the study, patients will be closely monitored, including evaluation of injection sites, laboratory monitoring for liver function test abnormalities, renal function, plasma and urine glycolate levels, and 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, women of childbearing potential participating in the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol.

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 safety data from the ongoing clinical study (ALN-GO1-001) and nonclinical studies, the benefit-risk assessment is positive and supports the evaluation of lumasiran in a Phase 3 study in pediatric and adult patients with PH1.

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

2. OBJECTIVES AND ENDPOINTS

Primary	
• To evaluate the effect of lumasiran on percent reduction in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate excretion from baseline to Month 6
Secondary	
• To characterize the effect of lumasiran on absolute levels of urinary oxalate excretion, oxalate:creatinine ratios, and plasma oxalate • To evaluate the effect of lumasiran, on renal function • To evaluate the long-term treatment effect of lumasiran	• Absolute change in 24-hour urinary oxalate corrected for body surface area (BSA) from baseline to Month 6 • Change in 24-hour urinary oxalate:creatinine ratio (value/upper limit of normal [ULN]) from baseline to Month 6 • Proportion of patients with 24-hour urinary oxalate level at or below 1.5 x ULN at Month 6 • Proportion of patients with 24-hour urinary oxalate level at or below ULN at Month 6 • Percent change in plasma oxalate from baseline to Month 6 • Absolute change in plasma oxalate from baseline to Month 6 • Change in estimated glomerular filtration rate (eGFR) from baseline to Month 6 • Change from baseline (percent and absolute) in 24-hour urinary oxalate excretion, percentage of time that 24-hour urinary oxalate is $\leq 1.5 \times$ ULN, 24-hour urinary oxalate:creatinine ratios and eGFR in the extension periods
Exploratory	
• To evaluate quality of life (QoL) • To evaluate the change in nephrocalcinosis and renal stones • To evaluate the additional pharmacodynamic (PD) parameters of	• Change in Kidney Disease Quality of Life Questionnaire (KDQOL) for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL [the generic and

plasma glycolate, urinary glycolate, and urinary oxalate in spot urine collections • To characterize the pharmacokinetics (PK) of lumasiran • To assess for antidrug antibodies (ADA) against lumasiran • To evaluate the effects of lumasiran on patient and caregiver resource use • To describe the patient experiences on lumasiran in PH1 patients and the experiences of caregivers for these patients	ESRD modules]) for patients <18 years of age at screening • Change in Euro Quality of Life Health State Profile Questionnaire (EQ-5D) and EQ-5D Visual Analog Scale (VAS) • Change in rate of renal stone events • Change in nephrocalcinosis as assessed by renal ultrasound • Change in urinary and plasma glycolate • Change in urinary oxalate:creatinine ratios as assessed in random spot urine collections • PK profile of lumasiran • Frequency of ADA • Change in patient resource use (eg, work/school attendance, visits to doctor/hospital) • Change in patient and caregiver experiences as evaluated by patient and caregiver experience surveys
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency and seriousness of adverse events (AEs) during the 6-month double-blind treatment period and in the extension periods

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of lumasiran in patients with PH1 ≥6 years of age with relatively preserved renal function. The study will be conducted in 3 parts: a 6-month, placebo-controlled, double-blind treatment period followed by a 3-month blinded treatment extension period and an open-label extension period of up to 51 months. A schematic of the study design is shown in Figure 1.

Patients will be screened within 60 days prior to study drug administration. At least three 24-hour urine collections will be completed during the screening period to assess urinary oxalate excretion. Patients must provide valid collections (see Section 6.3.1.1) for at least 2 urine collections prior to dosing on Day 1. The mean urinary oxalate excretion from the first 2 valid

baseline collections will be used to determine eligibility for the study, defined as urinary oxalate excretion of ≥0.70 mmol/24h/1.73m^2.

Consenting (and assenting, where applicable) patients who meet all eligibility criteria will be randomized 2:1 to receive their first dose of subcutaneously administered lumasiran or placebo on Day 1. Treatment groups will be stratified at randomization by mean urinary oxalate excretion from the first 2 valid baseline collections (see Section 3.5).

During the 6-month, placebo-controlled, double-blind treatment period, patients will receive loading doses of 3.0 mg/kg lumasiran or placebo administered monthly for 3 doses (at Day 1, Month 1, and Month 2) followed by the first maintenance dose of 3.0 mg/kg lumasiran or placebo administered at Month 3 and then once every 3 months.

After the Month 6 visit assessments are completed (ie, end of the 6-month double-blind treatment period), patients from both treatment arms (lumasiran and placebo) will begin the 3-month blinded treatment extension period, in which all patients will receive active drug. To maintain the blind to treatment assignment, study drug will continue to be administered in a double-blind manner and at the same frequency as in the 6-month double-blind period. In the 3-month treatment extension period, patients will receive study drug according to initial treatment assignment as follows:

- Patients who had been randomized to placebo will receive 3.0 mg/kg lumasiran monthly at Months 6, 7, and 8
- Patients who had been randomized to lumasiran will be given 3.0 mg/kg lumasiran at Month 6 and placebo at Months 7 and 8
- All patients will be given a maintenance dose of lumasiran at Month 9 and then once every 3 months thereafter

Assessments of efficacy and safety will be conducted during visits to the clinical study center every 2 weeks for the first month of this part of the study and monthly thereafter through Month 9.

Patients will receive their first open-label dose of lumasiran at Month 9 to begin their participation in the open-label extension (OLE) part of the study, in which they will be treated with lumasiran administered once every 3 months for up to 48 months; patients will receive their last dose of lumasiran at Month 57. Patients entering the OLE period will undergo efficacy and safety assessments every 3 months through Month 24, and every 6 months until the end of study (EOS) visit at Month 60.

Starting at Month 15, once all patients are expected to be on a stable regimen of lumasiran once every 3 months, where applicable country and local regulations and infrastructure allow, study drug administration may be administered by a home healthcare professional for patients who have demonstrated the ability to tolerate the study drug.

24-hour urine collections will be performed for evaluation of oxalate excretion. At the Month 6 and Month 12 visits, patients will provide at least three 24-hour urine collections and ≥2 of these collections must be valid (see Section 6.3.1.1) prior to completion of the Month 6 and Month 12 visit assessments. Single 24-hour urine collections will be obtained for the study visits specified

in the Schedules of Assessments. Details on 24-hour urine collection procedures are included in Section 6.3.1.

An external, independent DMC will monitor safety over the course of the study. Details for the committee will be provided in DMC charter.

3.2. Duration of Treatment

The duration of treatment with study drug is up to 5 years, including a 6-month double-blind treatment period followed by a 3-month blinded treatment extension period, and up to a 51-month open-label extension period.

3.3. Duration of Study

The estimated total time on study, inclusive of screening, for each patient is up to 62 months, including up to 2 months of screening followed by up to 60 months of treatment (see Section 3.2).

3.3.1. Definition of End of Study for an Individual Patient

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

- the patient has completed the end of study (EOS; Month 60) visit, or
- the patient has completed the safety follow-up visits until PD recovery of 24-hour urinary oxalate is >70% of baseline, and plasma glycolate is <30% above baseline or ≤ the ULN, or
- the patient has completed 12 months of monitoring following the final lumasiran dose.

3.4. Number of Planned Patients

The planned enrollment for this study is 30 patients.

3.5. Method of Assigning Patients to Treatment Groups

Using the Interactive Response System (IRS), patients will be randomized 2:1 to the lumasiran or placebo arm. Randomization will be stratified by mean baseline urinary oxalate level (>1.70 mmol/24h/1.73m^2 versus ≤1.70 mmol/24h/1.73m^2). The mean urinary oxalate level for stratification will be calculated using the values obtained from the first 2 valid baseline 24-hour urine collections.

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 IRS. The Investigator or his/her designee will contact the IRS to randomize the patient after confirming that the patient fulfills all the inclusion criteria and none of the exclusion criteria.

3.6. Blinding

All site personnel (with the exception of some site pharmacists) and patients (including their families or caregivers) will be blinded to study drug treatment assignment until the last patient completes the assessments at the Month 9 visit. Site pharmacists may be unblinded to study drug treatment only where required by documented pharmacy procedure. All Sponsor personnel with direct oversight of the conduct and management of the study (except for staff involved in randomization and study drug supply) will be blinded to study drug treatment until the 6-month treatment period data is unblinded for the primary analysis. Sponsor personnel who may have treatment assignment information will not have access to patient level data from the clinical trial databases.

The independent DMC and an independent biostatistics group will have access to patient level treatment assignments.

To maintain the blind to treatment assignment, during the 3-month blinded treatment extension period, study drug will continue to be administered in a double-blind manner and at the same frequency as in the 6-month double-blind period. However, the study is designed so that all patients will receive active drug during the extension period according to initial treatment assignment as follows:

- Patients randomized to placebo: 3.0 mg/kg lumasiran administered as monthly loading doses (Month 6, 7, and 8)
- Patients randomized to lumasiran: 3.0 mg/kg lumasiran administered as a single maintenance dose at Month 6

Therefore, all site personnel and patients will be aware that all patients will receive active drug administered at Month 6 even though all doses of study drug will be masked.

The Sponsor and all site personnel will be blinded to central laboratory results of urinary and plasma oxalate and glycolate from after the time of the first dose until unblinding. Results will not be reported to the Investigator from the first dose to until the last patient completes the assessments at the Month 9 visit. In addition, Investigators and staff involved with this trial and all medical staff involved in the patient's medical care should refrain from obtaining local oxalate or glycolate measurements until the sites and patients are unblinded, or until the patient ends the study, whichever is earlier. If oxalate or glycolate is measured during the blinded period, all reasonable steps must be undertaken to avoid informing the patient and site personnel of the results until the sites and patients are unblinded.

A list of all Alnylam personnel or personnel working on behalf of Alnylam who are unblinded to study data will be maintained in the trial master file (TMF). Any unplanned unblinding occurring during the study period will be documented and reported in the clinical study report.

Additional details are provided in a separate blinding plan.

3.6.1. Emergency Unblinding

If the treating physician determines that the clinical management of the patient requires knowledge of the study drug assignment, the Investigator may break the blind, as necessary. If time permits, clinical study center personnel should contact the Medical Monitor before

unblinding to discuss the need to unblind the patient, but must do so within 1 working day after the unblinding event. Unblinding information should be limited to the fewest number of people on a need-to-know basis. A record of when the blind was broken, who was unblinded, who broke the blind, and why it was broken, will be maintained in the TMF.

Refer to the IRS instructions for details on unblinding.

3.7. Data Monitoring Committee

An external independent DMC will oversee the safety and overall conduct of this study. The DMC will operate under the rules of a charter that will be reviewed and approved at the organizational meeting of the DMC. Details are provided in the DMC Charter.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

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

Age

1. Age 6 years or older.

Patient and Disease Characteristics

2. Documentation or confirmation of PH1 as determined by genetic analysis prior to randomization.
3. Mean 24-hour urinary oxalate excretion from the first 2 valid 24-hour urine collections is $\geq$0.70 mmol/24h/1.73m^2
4. If taking pyridoxine (vitamin B6) for the treatment of PH1, must have been on stable regimen for at least 90 days before randomization, and willing to remain on this stable regimen for 12 months from first study drug administration.

Informed Consent

5. Patient is able to understand and 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.

4.2. Exclusion Criteria

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

Disease-specific Conditions

1. Medical history includes clinical evidence of extrarenal systemic oxalosis, as determined by the Investigator.

Laboratory Assessments

2. Has any of the following laboratory parameter assessments at screening:

a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × upper limit of normal (ULN)
b. Total bilirubin >1.5 x ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 x ULN
c. International normalized ratio (INR) >1.5 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)

3. Has known active human immunodeficiency virus (HIV) infection; or evidence of current or chronic hepatitis C virus (HCV) or hepatitis B virus (HBV) infection
4. Estimated GFR of <30 mL/min/1.73m^2 at screening (calculation will be based on the Modification of Diet in Renal Disease [MDRD] formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age) See Section 10.1

Prior/Concomitant Therapy

5. 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 prior to randomization

Medical Conditions

6. History of renal or liver transplant
7. Has other medical conditions or comorbidities, which in the opinion of the Investigator, would interfere with study compliance or data interpretation
8. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
9. History of intolerance to subcutaneous (SC) injection(s)

Contraception, Pregnancy, and Breastfeeding

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

Alcohol Use

12. 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]
13. History of alcohol abuse, within the last 12 months before screening, in the opinion of the investigator.

4.3. Removal from Therapy or Assessment

Patients or their legal guardians are free to discontinue study drug and/or stop participation in the study at any time and for any reason, without penalty to their continuing medical care. The Investigator or the Sponsor may 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 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

The Investigator, or designee, may discontinue study drug in a patient, if the patient:

- Is in significant violation of the protocol
- Experiences a serious or intolerable AE
- Is non-adherent to treatment regimen
- Becomes pregnant
- Is lost to follow-up
- Has another reason (non-adverse event)
- Or, the study is terminated by the Sponsor

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 6.5.7.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be subsequently confirmed by a serum pregnancy test prior to discontinuing the study drug.

If a patient discontinues dosing due to an adverse event (AE), including serious adverse events (SAEs), the event should be followed as described in Section 6.5.7. When a patient discontinues study drug dosing, the primary reason must be recorded in the appropriate section of the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgment, as applicable.

Patients who discontinue from study drug prior to completion of the Month 6 assessments will be encouraged to remain on study and complete monthly assessments (including 24-hour urine collections, but excluding PK assessments) through Month 6. They will then be asked to complete safety follow-up visits once every 3 months per the safety follow-up schedule (see Table 2). Patients who discontinue study drug after completion of the Month 6 assessments 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 thereafter per the safety follow-up schedule (see Table 2).

While the study sites and patients remain blinded, the patient will be followed until 12 months after the last dose of lumasiran. If the patient is still in follow-up at the time when sites and patients are unblinded, PD recovery should be evaluated to determine if the patient meets the PD recovery criteria (ie, 24-hour urinary oxalate is >70% of baseline, and plasma glycolate is <30% above baseline or ≤ the ULN) and is eligible to stop study follow-up.

4.3.2. Stopping a Patient's Study Participation

A patient or their legal guardian may stop participation in the study at any time. Patients considering stopping their participation in the study during the blinded period of the study should be informed that they can discontinue study drug and complete their study assessments through the Month 6 visit and complete safety follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or their legal guardian consents. If a patient or their legal guardian chooses to discontinue study drug and stop participation in all follow-up prior to the completion of the Month 6 visit, every effort should be made to conduct the assessments scheduled to be performed at the Month 6 visit and the safety follow-up assessments (see Table 1).

Patients or their legal guardians considering stopping participation in the study after the sites have been unblinded should be informed that they can discontinue study drug and complete safety follow-up visits as described in Section 4.3.1, or alternatively may complete any minimal assessments for which the patient or legal guardian consents.

If a patient or their legal guardian still chooses to stop participation in the study, every effort should be made to conduct the ET assessments prior to stopping study participation (see Table 2).

The patient may decide to withdraw consent, 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 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.

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 is best maintained if all enrolled patients continue study assessments and follow-up even if study drug is discontinued.

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the 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 adverse event (AE), including SAEs, the event should be followed as described in Section 6.5.7.

Patients stopping participation in the study will be asked if they are willing to consent to either be contacted by telephone or to allow non-patient contact follow-up (eg, medical record review) up to 6 years after enrolling onto the study to document their overall health status.

4.3.3. Replacement of Study Patients

Patients who discontinue the study drug or stop participation in the study will not be replaced.

4.3.4. 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 fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to 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 (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, the patient will be considered to have stopped participation in the study.

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 and placebo 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.

The control drug for this study will be a placebo (sodium chloride 0.9% w/v for SC administration). Placebo will be provided by the Sponsor; it will be packaged identically to lumasiran.

5.2.2. Dose and Administration

Study drug is administered based on total body weight. 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 the 6-month double-blind treatment period (Day 1 through Month 6 assessments), patients will be administered loading doses of 3.0 mg/kg lumasiran or an equivalent volume of placebo as an SC injection once monthly for 3 doses (administered at Day 1, Month 1, and Month 2 visits) followed by 1 maintenance dose of 3.0 mg/kg lumasiran or placebo administered at the Month 3 visit. During the 3-month blinded treatment extension period (from dosing at Month 6 [following completion of all assessments] through Assessments at Month 9), patients randomized to placebo will be administered loading doses of 3.0 mg/kg as an SC injection once monthly for 3 doses (administered at Month 6, Month 7, and Month 8 visits). Patients randomized to lumasiran will continue to receive a maintenance dose at the Month 6 visit.

Patients randomized to lumasiran will receive doses of placebo administered at the Month 7 and Month 8 visits to keep all procedures same between the lumasiran and placebo arm patients and maintain the blind.

In order to maintain the blind to treatment assignment, study drug will continue to be administered in the blinded treatment extension period in a double-blind fashion. However, due to study design features, both patients and study site personnel will be aware that all patients will receive active drug at Month 6. Patients will receive their first open-label maintenance dose of lumasiran at Month 9.

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. The injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and 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.

From Month 15 through the end of the study, study drug administration may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow, after consultation with the medical monitor. 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 a patient does not receive a dose of study drug 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 doses of study drug, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue the study (see also Section 4.3).

Additional details can be found in the Pharmacy Manual.

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. LFT Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. LFT results from the previous visit should be reviewed prior to dosing.
2. For any ALT or AST elevation >3× ULN central laboratory results should be used to guide subsequent monitoring as detailed in Table 6.
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 6 and Table 9.

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 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 6 (below):

Table 6: 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 9 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 8
	• Monitor at least every two weeks: hematology, serum chemistry, LFT, and coagulation per Table 8.
	• If elevation persists for ≥2 months, must discuss with the medical monitor before continuing dosing

>5× to 8× ULN	• Hold study drug 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 9 (all assessments to be performed once)
	  • Hematology, serum chemistry, LFT, and coagulation per Table 8
	• Monitor at least weekly: hematology, serum chemistry, LFT, and coagulation per Table 8 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 of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; INR=international normalized ratio; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

5.2.4. Preparation, Handling, and Storage

Staff at each clinical study center or the home healthcare professional will be responsible for preparation of study drug doses, according to procedures detailed in the Pharmacy Manual. 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] until dose preparation. Deviations from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee, as described in the Pharmacy Manual.

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.

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

Use of concomitant medications will be recorded on the patient's eCRF as specified in the Schedules of Assessments (see Table 1 and Table 2). This includes all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals. Any changes in medications during the study will also be recorded in the eCRF.

If patients use NSAIDs 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 stable regimen for at least 90 days before randomization, and willing to remain on this stable regimen for 12 months from first study drug administration. Patients should avoid high dose vitamin C preparations within 4 days prior to oxalate assessments.

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

Patients may be treated for PH1 according to local standard of care. Patients should continue their current standard of care regimen, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy for the first 12 months of the study. Standard of care treatment may be adjusted beginning at Month 12 in accordance with clinical judgement. If pyridoxine therapy is discontinued, pyridoxine levels should be assessed for at least the next 2 study visits.

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 eCRF. 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 or trained home healthcare professionals.

5.5. Other Requirements

5.5.1. Contraception

Women of child-bearing potential must be willing to use acceptable methods 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 contraception at menarche or must discontinue study drug.

Birth control methods which are considered acceptable 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, implantable, injectable, or transdermal hormonal methods of contraception. Women of child-bearing potential who use hormonal contraceptives as a method of contraception must also use a barrier method (condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [eg, foam, gel, film, cream, or suppository]).
- If hormonal methods of contraception are medically contraindicated due to their underlying disease, a double-barrier method (combination of male condom with cap, diaphragm, or sponge, in conjunction with spermicide) is also considered an acceptable method 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 until study completion.

Women 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 males of contraception (condom) may be required in some countries, e.g., France, in order to comply with local requirements as described in the corresponding patient informed consent forms.

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

5.5.2. Alcohol Restrictions

Patients will limit alcohol consumption throughout the course of the study. Alcohol is limited to no more than 2 units per day (unit: 1 glass of wine [approximately 125 mL] = 1 measure of spirits [approximately 1 fluid ounce] = ½ pint of beer [approximately 284 mL]) for the duration of the study.

5.5.3. 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 is provided in Table 1, Table 2, Table 3, and Table 4. Study assessments for pregnancy test (urine or serum), clinical lab assessments, urine collection, and DNA testing may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow.

6.1. Screening Assessments

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 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).

Patient demographic data and medical history/disease history will be obtained. 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 PH1/*AGXT* mutation analysis will be collected for patients who do not have documented PH1 genetic analysis to confirm eligibility.

During the screening period, at least 3 separate 24-hour urine collections will be completed to assess urinary oxalate excretion. Patients are strongly encouraged to complete these collections during supervised visits unless they are already familiar with the collection procedures. At least 2 of these collections need to be confirmed to be valid collections (see Section 6.3.1.1) prior to receiving study drug on Day 1. The mean urinary oxalate excretion from the first 2 valid baseline collections will be used to determine eligibility for the study (see Section 4.1) and randomization stratification.

6.1.1. Retesting

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

6.1.2. Rescreening

A patient who does not meet all study eligibility criteria may be allowed to return for rescreening if appropriate in the opinion of the investigator and after consultation with the Medical Monitor. A patient will be re-consented and assent obtained (if applicable) if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

6.2. Efficacy Assessments

The efficacy of lumasiran will be assessed by evaluating the percent change in 24-hour urinary oxalate excretion determined from 24-hour urine sample collections described in Section 6.3.1.

6.3. Pharmacodynamic and Renal Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma and urinary oxalate and glycolate concentrations) and renal parameters at the time points specified in the Schedules of Assessments (Table 1 and Table 2). All blood and urine samples will be collected prior to dosing, if applicable.

Where local regulations allow and infrastructure is in place, home nursing may be used to collect urine samples or for repeat blood sample collection, if necessary.

6.3.1. 24-hour Urine Collections to determine Urinary Oxalate Excretion

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 (Table 1 and Table 2) to assess urinary oxalate excretion. Urinary oxalate concentrations will be analyzed centrally using a validated assay. The duration of collection and volume of urine in the collection will be

recorded in the eCRF. An aliquot of the 24-hour urine collection will also be used to determine urinary creatinine content to determine if the 24-hour urine collections need to be repeated (see Section 6.3.1.1).

Single void collections for random urine sample for PD analysis should be collected as a first morning void when possible.

Table 7 shows the 24-hour urine collection procedure by study visit.

Table 7: 24-hour Urine Collection Procedure by Study Visit

Study Visit and Urine Collection Window	Number of Collections to Schedule	Validity Requirement Prior to Dosing (see Sec 6.3.1.1)	Option for Catheterized Collection?	Notes
Screening (within 60-day period)	3	2 valid collections prior to dosing	No	Supervised collections are encouraged unless patient already familiar with collection procedure. If any collections are invalid, the remaining collections for screening must be supervised.
Month 6 and Month 12 (within 14 days prior to dosing)	3	2 valid collections prior to dosing	Yes	If a patient has had ≥2 prior invalid collections, all 3 collections must be supervised. At least 2 valid collections must be obtained prior to dosing. If any collections for the timepoint are invalid, the remaining collections for the timepoint must be supervised.
Interim Monthly Visits with Dosing (Months 1-3 and Months 7-9 [within 7 days prior to dosing])	1	No	Yes	If invalid collection is obtained for the timepoint, single repeat collection must be supervised. Repeat collection validity results are not required prior to dosing.
Interim Monthly Visits Without Dosing (Month 4 and Month 5 [within 7 days prior to visit])	1	No	Yes	If invalid collection is obtained for the timepoint, single repeat collection must be supervised. Repeat collection, if necessary, is to be completed within ±7 days of the visit.
Visits after Month 12 (within 14 days prior to visit)	1	No	Yes	If collection is invalid for the timepoint, single repeat collection must be obtained within ±14 days of the visit. Dose should not be held if validity results unknown prior to dosing.
Safety Follow-up Visits (within ±7 days of visit)	1	No	Yes	Repeat collections are optional.

Abbreviations: Sec=section

Notes:

- Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine is not a supervised collection, patients may either bring 24-hour urine collections to the clinic or have it couriered to the designated laboratory.
- Optional catheterized collections are permitted at any visit after initial study drug administration at the discretion of the Investigator with agreement of patient and/or legal guardian, if applicable.

6.3.1.1. Validity Criteria for 24-hour Urine Collections

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

- The collection is between 22-26 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 as indicated by the patient's urine collection diary.
- The 24-hour creatinine content is at least 10 mg/kg as assessed by the central laboratory.

6.3.1.2. Urinary Oxalate:Creatinine Ratio

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

6.3.2. Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR will be obtained at the time points specified in the Schedules of Assessment (Table 1 and Table 2). eGFR (mL/min/1.73m^2) will be calculated to assess renal function during the study. The calculation will be based on the Modification of Diet in Renal Disease (MDRD) formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age at screening (Appendix 10.1).[17, 18]

6.3.3. Renal Stone Events

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

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

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

Since renal stone events are recorded as an efficacy assessment for lumasiran, these will not be treated as AEs or SAEs. However, if a patient experiences other AEs or SAEs during a renal stone event, they should be reported (see Section 6.5.7.1).

6.3.4. Sample Analysis

All PD assessments will be analyzed centrally. Details on the blinding of study results are provided in Section 3.6.

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

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of lumasiran PK parameters including metabolites (as necessary) at the time points indicated in the Schedules of Assessments (Table 1 Table 2). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 3 and Table 4 (for patients at East Asian Study Centers; see Section 6.4.1).

The concentration of lumasiran in blood samples will be determined using a validated assay. Details regarding sample volumes to be collected, and the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

6.4.1. Pharmacokinetic Assessments in Patients at East Asian Study Centers

In patients who are in enrolled at East Asian sites, which include sites in China, Korea, Japan, Taiwan, and Hong Kong, blood and urine samples for PK analysis will be collected at the time points indicated in Table 4 and Table 5.

Plasma PK parameters such as C_{max}, t_{max}, $t_{½\beta}$, AUC, CL/F, and V/F will be calculated for the lumasiran plasma concentration profiles. In addition, urine PK parameters will be calculated using pooled urine samples collected over 24 hours from patients at East Asian study centers according to the schedule provided in Table 5.

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including serious adverse events (SAEs), recording of concomitant medication and measurements of vital signs, weight and height, physical examination, and electrocardiogram (ECG) findings and laboratory tests.

Safety will be monitored over the course of the study by a DMC as described in Section 3.7.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedules of Assessments (Table 1 and Table 2) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. On Day 1 and Month 6 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 in the seated or supine position, after the patient has rested comfortably for 10 minutes. Blood pressure should be taken using the same arm. 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 medially 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

Height will be measured in centimeters. For patients <18 years of age at the study visit, height will be measured in triplicate. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedules of Assessments (Table 1 and Table 2) and will be recorded in the eCRF. 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.

6.5.3. Physical Examination

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

Symptom-directed physical examinations will be guided by evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

Physical examination notes regarding any observed abnormalities will be recorded in the eCRF.

6.5.4. Electrocardiogram

12-lead ECGs will be obtained, as specified in the Schedules of Assessments (Table 1 and Table 2). Specific timepoints and details regarding the method of ECG acquisition (local/singlicate or central/triplicate) are provided in Table 3 and Table 4. Patients should be supine for at least 10 minutes before each ECG is obtained. Triplicate 12-lead ECGs will have readings approximately 5 minutes apart and will be centrally read.

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

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

6.5.5. Renal Ultrasound

Renal ultrasounds will be obtained, as specified in the Schedules of Assessments (Table 1 and Table 2). Renal ultrasound will be performed according to instructions provided in the Study Manual in a standardized manner. Renal ultrasounds will be reviewed centrally and those obtained at Screening and Month 6 will be read in a blinded manner.

6.5.6. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 5.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, or as per DMC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratories and assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 8 and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 2).

While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in Table 8 which are performed at the clinic should also be sent in parallel to the central laboratory. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results on samples drawn on the same day.

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

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 8: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the MDRD formula for adults [≥18 years of age at screening] or the Bedside Schwartz formula for children <18 years at screening)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Pyridoxine (vitamin B6)[a]	
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Coagulation	
Prothrombin time	International normalized ratio
Partial thromboplastin time	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; MDRD=modification of diet in renal disease; PH1=primary hyperoxaluria type 1; RBC=red blood cell

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

6.5.6.1. 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 Assessments (Table 1 and Table 2). A blood sample to evaluate antidrug antibodies will be collected at the Early Termination (ET) visit, if applicable.

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

6.5.6.2. Pregnancy Testing

A pregnancy test will be performed for women of child-bearing potential, and for pediatric/adolescent females upon initiation of menarche. A serum pregnancy test will be performed at Screening or upon initiation of menarche, if applicable, and urine pregnancy tests will be performed thereafter per the Schedules of Assessments and any time pregnancy is suspected. 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. Any woman 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 6.5.7.7 for follow-up instructions).

6.5.6.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 5.2.3.1. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 9 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments from Table 8, and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for withholding the study drug, are described in Section 5.2.3.1.

Table 9: Hepatic Assessments in Patients Who Experience Elevated Transaminases

Extended Hepatic Panel	
Herpes Simplex Virus 1 and 2 antibody IgM, IgG	Herpes Zoster Virus IgM, IgG
HIV 1 and 2[a]	HHV-6
Cytomegalovirus antibodies, IgM, IgG	HBs Ag, HBc antibody IgM and IgG
Anti-nuclear antibodies	Epstein-Barr Virus antibodies, IgM and IgG
Anti-smooth muscle antibodies	Anti-mitochondrial antibodies
HCV antibody	HAV antibody IgM
HCV RNA PCR – qualitative and quantitative	HEV antibody IgM
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
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; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

- All assessments will be measured in central laboratory. The full panel of assessments should only be performed once; individual assessments may be repeated, as needed.

[a] HIV testing will not be performed where prohibited by local regulations.

6.5.6.4. 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 10 from the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document (Section 10.2 in the Appendix).[19] Collections per the SOA do not exceed the maximum 24-hour or 30-day volume limits for a 15 kg child who is not at an East Asian site. At East Asian sites, if a patient weighs less than 30 kg, then PK blood samples should be limited to 1 ml at each time point and the blood samples for exploratory analyses should not be drawn.

6.5.7. Adverse Events

6.5.7.1. Definitions

Adverse Event

According to the International Council on Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event

(AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

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

Serious Adverse Event

A serious adverse event (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 in-patient 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). Reactions with onset and resolution within 4 hours of the injection (eg, transient pain/burning at injection site) do not meet the study definition of ISRs, unless immediate treatment is required. 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 6.5.7.2 and Section 6.5.7.3 , respectively.

Adverse Event Severity

Adverse events 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 adverse event.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events 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.

6.5.7.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient and legal guardian, if applicable, should be asked about medically relevant changes in the patient's health since the last visit. The patient and legal guardian, if applicable, 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.

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) in both the eCRF and the SAE form.

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

For AEs that are considered AEs of clinical interest (Section 6.5.7.1), the Sponsor or its designee should be notified within 24 hours using a supplemental AEs of Clinical Interest eCRF. 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 a supplemental ISR eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, event outcome).

6.5.7.4. 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 6.5.7.1 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 SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update 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.

6.5.7.5. 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.

6.5.7.6. 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.

6.5.7.7. 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 6.5.7.4.

6.5.7.8. 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. 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.

6.6. 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.

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, a set of biological specimens will be collected at the timepoints indicated in the Schedule of Assessments (Table 1).

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.

Where allowed per local regulations, ethics committee (IRB/EC) approval, and patient consent (and assent, where applicable), the samples will be collected as part of this study. Potential exploratory investigations may include DNA, RNA or biochemical metabolite assessments as they relate to disease progression, efficacy or safety.

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, patients/subjects will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

6.7. Quality of Life (QOL)

QOL questionnaires will be used to evaluate overall health status and quality of life at the timepoints listed in Table 1 and Table 2. The age of the patient at screening will determine which age-specific questionnaires will be utilized for the duration of the study.

QOL assessments include the following:

- Kidney disease Quality of Life Questionnaire (KDQOL), specifically the KDQOL-36 for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL), including the generic and ESRD modules (parent and/or self-report versions) [20] for patients <18 years of age at screening.
- EQ-5D: a standardized instrument consisting of a questionnaire and a visual analog scale pertaining to 5 dimensions. Scoring of the questionnaire is based on degrees of disability. Scoring of the visual analog scale 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. The EQ-5D-5L questionnaire will be utilized in patients ≥18 years of age at screening, and the EQ-5D-Y questionnaire will be utilized in patients <18 years of age at screening, where available.[21]

6.8. Patient and Caregiver Experience Surveys

The patient and caregiver experience surveys assess patients' experience living with PH1, including their experience with PH1 treatments, as well as the effect of PH1 on patients' caregivers. These surveys will be completed at the time points specified in the Schedules of Assessment (Table 1 and Table 2) and each take approximately 10 minutes to complete.

For the Patient Experience Survey, patients ≥13 years of age at screening will complete the survey themselves if they are able. If the patient is unable to complete the Patient Experience Survey alone, their caregiver or site staff may complete the survey for 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. Additionally, for patients under legal age of consent at the time of screening, their caregiver will also 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.

6.9. 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. This questionnaire will be completed at the time points specified in the Schedules of Assessment (Table 1 and Table 2) and takes approximately 10-12 minutes to complete.

Patients ≥13 years of age at screening will complete the questionnaire themselves 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-reported information related to hospitalizations, urgent healthcare visits, procedures and surgeries.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized prior to database lock. The plan will detail the implementation of the statistical analyses in accordance with the principle features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for the study is 30 patients.

Patients will be randomized 2:1 to receive lumasiran or placebo, respectively. Assuming the mean percent reduction from baseline to Month 6 in 24-hour urinary oxalate corrected for body surface area (BSA) is 17% in the placebo arm and the standard deviation in both arms is 25%, 24 patients will provide 90% power to detect a treatment difference of 37% at a 2-sided 5% significance level (ie, 54% reduction in the lumasiran arm). To account for potential drop-outs, 30 patients are planned to be enrolled in the study.

7.2. Statistical Methodology

The statistical and analytical plans presented below are brief summaries of planned analyses. More complete plans will be detailed in the statistical analysis plan (SAP). Changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. For information on study endpoints, see Section 2.

7.2.1. Populations to be Analyzed

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- Per-protocol (PP) Set: All randomized patients who received any amount of study drug, had baseline and at least one post-baseline 24-hour urinary oxalate, and did not experience any major protocol deviations that may impact the efficacy results within the 6-month double-blinded period. Patients will be analyzed according to the randomized treatment arms.
- Safety Analysis Set: All patients who received any amount a of study drug. Patients will be analyzed according to the treatment actually received.
- PK Analysis Set: All patients who received at any amount of study drug and have at least 1 PK concentration measurement.
- All Lumasiran Treated Set: All patients who received any amount of lumasiran including patients who took lumasiran during the 6-month double-blinded period and patients who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period.

The primary population used to evaluate efficacy will be the Full Analysis Set for the primary endpoint and secondary endpoints during the double-blind period. Safety during the double-blind period will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to evaluate the PK endpoints. The All Lumasiran Treated Set will be used to summarize the long-term efficacy and safety of lumasiran.

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, particularly for the 24-hour urinary oxalate assessments. Details will be provided in the SAP.

7.2.4. Baseline Evaluations

Demographics and other disease-specific baseline characteristics will be summarized descriptively by treatment arm and overall for the FAS and Safety Analysis Set.

7.2.5. Efficacy Analyses

7.2.5.1. Primary Endpoint

The primary endpoint is to compare the percent change from baseline to Month 6 in 24-hour urinary oxalate corrected for BSA between the treatment groups in the Full Analysis Set. The analysis will be performed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in urinary oxalate corrected for BSA. The model includes baseline value as covariate and fixed effect terms including treatment arm and visit (Months 3, 4, 5, 6). The treatment estimates from this model will represent an average percent change from baseline of 24-hour urinary oxalate excretion across months 3 through 6 at which the treatment effect is expected to have reached steady state. Furthermore, given the variability of 24-hour urinary oxalate, averaging the values across these visits will yield stable treatment estimates.

Baseline and Month 6 urinary oxalate values are planned to be collected in triplicate (minimum requirement of duplicate) and the calculated median of valid collections during each time period (visit) will be used in the analysis. BSA will be calculated using the Mosteller formula.

Sensitivity analyses will be conducted to assess the robustness of the estimates and will be detailed in the SAP.

A patient is considered to have completed the primary outcome measure at the time of completion of the Month 6 assessments.

7.2.5.2. Secondary Endpoints

To control the overall type I error, these secondary endpoints will be tested in the following hierarchical order:

- Absolute change in 24-hour urinary oxalate corrected for BSA from baseline to Month 6
- Change in 24-hour urinary oxalate:creatinine ratio (value/ULN) from baseline to Month 6
- Proportion of patients with 24-hour urinary oxalate level at or below 1.5 x ULN at Month 6
- Proportion of patients with 24-hour urinary oxalate level at or below ULN at Month 6
- Percent change in plasma oxalate from baseline to Month 6

- Absolute change in plasma oxalate from baseline to Month 6

Continuous endpoints will be analyzed using an MMRM approach similar to the one described for the primary endpoint. Binary endpoints will be analyzed using the Cochran-Mantel-Haenszel test stratified by baseline urinary oxalate. The odds ratio and the differences in proportions with corresponding 95% confidence will also be summarized.

Secondary endpoints assessed beyond Month 6 will be summarized descriptively. Change in eGFR over time will also be summarized descriptively.

7.2.5.3. Exploratory Endpoints

Details will be described in the SAP.

7.2.6. Pharmacodynamic Analysis

Analysis of the PD parameters are specified in Section 7.2.5.2. Any PD parameters not already prespecified for testing will be summarized descriptively.

7.2.7. Pharmacokinetic Analysis

Population pharmacokinetic analysis will be performed to describe the plasma concentration profiles of lumasiran. The impact of relevant patient covariates such as age, weight, race, gender, hepatic impairment, and renal impairment on the PK of lumasiran will be assessed using population PK approach.

For patients enrolled in East Asian centers with 24-hour PK collection, pharmacokinetic analyses of plasma and urine will be conducted using noncompartmental methods. Plasma pharmacokinetic parameters including, but will not be limited to: 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 determine using noncompartmental approach. Other parameters may be calculated, if deemed necessary. In addition, relevant urine PK parameters will be calculated using 24-hour urine PK profiles.

7.2.8. Safety Analyses

The primary parameter is the frequency and seriousness of AEs. Safety parameters also include vital signs, ECGs, clinical laboratory assessments and physical exams. The extent of exposure will also be summarized. The primary summaries of the safety of lumasiran versus placebo will be based on safety parameters within the 6-month double-blind treatment period, using the Safety Analysis Set. Additional safety analyses will also be performed for the extension periods.

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

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

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

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

7.2.9. Immunogenicity Analyses

ADA results will be summarized descriptively.

7.2.10. Other Analyses

Other exploratory analyses will be detailed in the SAP.

7.2.11. Interim Analysis

No interim analysis is planned.

7.2.12. 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/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided. In the case of patients under the age of legal consent, legal guardian(s) must provide informed consent and the patient should provide assent per local regulations and institutional standards.

The patient's/legal guardian's signed and dated informed consent (or assent, if applicable) must be obtained before conducting any study tests or procedures that are not part of routine care. When a patient under the age of legal consent who has been enrolled in the study reaches the legal age of consent, the investigator must obtain the patient's informed consent prior to performing any further research interventions and/or procedures involving that patient.

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

8.1.2. Ethical Review

The study protocol, including the ICF (and 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. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form and 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 6.5.6.4. 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 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 randomized under the amended protocol, and patients/legal guardian must be re-consented to the most current version of the ICF (and 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 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, IEC/IRB 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, or its 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/1.73m^2) will be calculated from serum creatinine (SCr) based on the Modification of Diet in Renal Disease formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age.

Modification of Diet in Renal Disease Formula [17]

- 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)

Schwartz Bedside Formula [18]

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

10.2. Blood Volume Limits in Pediatric Patients

The maximum blood volume, which will be collected from pediatric patients over the course of the study, will be based on age and weight and will not exceed those specified in Table 10, which was adapted from the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document.

Table 10: Maximum Allowable Total Blood Volume Collection Chart

Body Weight	Body Weight	Total blood volume	Maximum allowable volume in a 24 hour		Total volume collected in a 30-day period	
			2.5% of total blood volume	3% of total blood volume	5% of total blood volume	10% of total blood volume
(kg)	(lbs)	(mL)	(mL)	(mL)	(mL)	(mL)
1	2.2	100	2.5	3	5	10
2	4.4	200	5	6	10	20
3	6.6	240	6	7.2	12	24
4	8.8	320	8	9.6	16	32
5	11	400	10	12	20	40
6	13.2	480	12	14.4	24	48
7	15.4	560	14	16.8	28	56
8	17.6	640	16	19.2	32	64
9	19.8	720	18	21.6	36	72
10	22	800	20	24	40	80
11-15	24-33	880-1200	22-30	26.4-36	44-60	88-120
16-20	35-44	1280-1600	32-40	38.4-48	64-80	128-160
21-25	46-55	1680-2000	42-50	50.4-60	64-100	168-200
26-30	57-66	2080-2400	52-60	62.4-72	104-120	208-240
31-35	68-77	2480-2800	62-70	74.4-84	124-140	248-280
36-40	79-88	2880-3200	72-80	86.4-96	144-160	288-320
41-45	90-99	3280-3600	82-90	98.4-108	164-180	328-3600
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.[19]

ALN-GO1-003 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 19 MARCH 2019

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

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to broaden the patient population by allowing enrollment of patients with a glomerular filtration rate ≥30 mL/min/1.73 m^2 and to align clinical objectives and endpoints across the Phase 3 program. A summary of the changes is outlined below.

The following inclusion criterion has been modified:

- Specify (to 2 decimals) the mean 24-hour urinary oxalate excretion as ≥0.70 mmol/24h/1.73m^2.

The following exclusion criterion has been modified:

- Change the exclusion threshold for the glomerular filtration rate from ≤45 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2.

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

- Clarify that the Month 12 visit spans 2 days in the Schedule of Assessments for the Open Label Extension Period (Table 2).
- Clarify that a predose PK sample is taken on the day of dosing in the PK assessment tables (Table 3 and Table 4).
- Add a rationale for the dosing regimen in patients with eGFR ≥30 mL/min/1.73 m^2.
- Update the secondary and exploratory objectives and endpoints, including changing the evaluation of the long-term effects of lumasiran and plasma oxalate levels from exploratory to secondary objectives and endpoints.
- Update the blinding rules to accommodate site pharmacies with established policies that do not support masking the study drug during transfer from vial to syringe.
- Clarify that additional liver function tests are performed when no alternative cause is identified.
- Add that male patients may be required to use contraception (condom) in some countries, such as France, to comply with local requirements.
- Clarify that specific study assessments may be conducted at a location other than the study center by a home healthcare professional.

- Add that patients may be rescreened per investigator judgment and after consultation with the Medical Monitor.
- Specify that pregnancy tests may be performed more frequently as per local requirements.
- Clarify that if the relationship between an AE and the study drug is at least reasonably possible, it is considered "related" to the study drug.
- Update the description of the quality of life questionnaires.
- Update the description of the analysis populations, how missing data are handled, and descriptions of the primary and secondary endpoints and analyses.
- Update the description of the pharmacodynamic analysis.
- Stipulate discontinuation criteria for the termination of the clinical trial or a clinical study site.
- Remove that an Institution or Investigator must wait 18 months to submit a publication once the primary manuscript has been published since the number of months varies per local requirements and this information is specified in the clinical trial agreement.

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

Table 1: Protocol Amendment 2 Detailed Summary of Changes

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

Purpose: Clarify that the Month 12 visit spans 2 days.

The change occurs in Table 2, Schedule of Assessments – Open Label Extension Period (After Month 9 through Year 5) (bullet in "Notes")

Added:
- **Gray-shaded column indicates the visit where assessments span 2 days.**

Purpose: Clarify that a predose PK sample is taken on the day of dosing.

The change occurs in Table 3, Pharmacokinetic and Electrocardiogram Assessment Time Points: All Sites except East Asian Sites (bullet in "Notes")

Added:
- **Predose samples are collected on the day of dosing.**

Sections also containing this change:

- Table 4, Pharmacokinetic and Electrocardiogram Assessment Time Points: East Asian Sites

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Purpose: Add a rationale for the dosing regimen in patients with eGFR ≥30 mL/min/1.73 m^2.

The primary change occurs in 1.4, Dose Rationale

Added: In patients with PH1, 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 relationship. For a given dose, the PK/PD model indicated that monthly administration leads to a more rapid decline in urinary oxalate levels relative to dosing every 3 months. A combination of monthly dosing in a loading phase and then dosing every 3 months in a maintenance phase achieves the goals of rapid and consistent lowering of urinary oxalate to normal or near normal levels in PH1 patients. **Preclinical and clinical data indicate the renal pathway is a minor elimination route for lumasiran. Thus, renal impairment is not expected to influence systemic exposure, PD, and safety properties of lumasiran, and no dose adjustments are needed based on renal function.** Thus, a lumasiran dosing regimen of 3.0 mg/kg once monthly for 3 doses followed by 3.0 mg/kg once every 3 months has been selected for this study in PH1 patients ≥6 years old with eGFR~~≥45~~ **≥30** mL/min/1.73 m^2.

Purpose: Update the secondary and exploratory objectives and endpoints, including changing the evaluation of the long-term effects of lumasiran and plasma oxalate levels from exploratory to secondary objectives and endpoints.

The primary change occurs in 2, Objectives and Endpoints

Now reads:

Primary	
• To evaluate the effect of lumasiran on percent reduction in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate excretion from baseline to Month 6
Secondary	
• To characterize the effect of lumasiran on absolute levels of urinary oxalate excretion~~and the~~ oxalate:creatinine ratios**, and plasma oxalate** • To evaluate the effect of lumasiran, on renal function • **To evaluate the long-term treatment effect of lumasiran**	• Absolute change in 24-hour urinary oxalate corrected for body surface area (BSA) from baseline to Month 6 • Change in 24-hour urinary oxalate:creatinine ratio (value/upper limit of normal [ULN]) from baseline to Month 6 • Proportion of patients with 24-hour urinary oxalate level **at or** below 1.5 x ULN at Month 6 • Proportion of patients with 24-hour urinary oxalate level **at or** below ULN at Month 6 • **Percent change in plasma oxalate from baseline to Month 6** • **Absolute change in plasma oxalate from baseline to Month 6** • Change in estimated glomerular filtration rate (eGFR) from baseline to Month 6 • **Change from baseline (percent and absolute) in 24-hour urinary oxalate excretion, percentage of**

	time that 24-hour urinary oxalate is ≤1.5 × ULN, 24-hour urinary oxalate:creatinine ratios and eGFR in the extension periods
Exploratory	
~~• To evaluate the long-term treatment effect of lumasiran~~ • To evaluate quality of life (QoL) • To evaluate the change in nephrocalcinosis and renal stones • To evaluate the additional pharmacodynamic (PD) parameters of ~~plasma oxalate~~plasma glycolate, urinary glycolate, and urinary oxalate in spot urine collections • To characterize the pharmacokinetics (PK) of lumasiran • To assess for antidrug antibodies (ADA) against lumasiran • To evaluate the effects of lumasiran on patient and caregiver resource use • To describe the patient experiences on lumasiran in PH1 patients and the experiences of caregivers for these patients	~~• Change from baseline (percent and absolute) in 24-hour urinary oxalate excretion, proportion of patients below ULN and 1.5 x ULN in 24 hour urinary oxalate levels, 24-hour urinary oxalate:creatinine ratios and eGFR in the extension periods~~ • Change in Kidney Disease Quality of Life Questionnaire (KDQOL) for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL [the generic and ESRD modules]) for patients <18 years of age at screening • Change in Euro Quality of Life Health State Profile Questionnaire (EQ-5D) and EQ-5D Visual Analog Scale (VAS) • Change in rate of renal stone events • Change in nephrocalcinosis as assessed by renal ultrasound • Change in urinary and plasma glycolate ~~• Change in plasma oxalate~~ • Change in urinary oxalate:creatinine ratios as assessed in random spot urine collections • PK profile of lumasiran • Frequency of ADA • Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

	• Change in patient and caregiver experiences as evaluated by patient and caregiver experience surveys
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency and seriousness of adverse events (AEs) during the 6-month double-blind treatment period and in the extension periods

Section also containing this change:

- Synopsis

Purpose: Update the blinding rules to accommodate those site pharmacies whose established policy does not support masking study drug during transfer from vial to syringe.

The change occurs in occurs in Section 3.6, Blinding

Now reads: All site personnel **(with the exception of some site pharmacists)** and patients (including their families or caregivers) will be blinded to study drug treatment **assignment** until the last patient completes the assessments at the Month 9 visit. **Site pharmacists may be unblinded to study drug treatment only where required by documented pharmacy procedure.** All Sponsor personnel with direct oversight of the conduct and management of the study (except for staff involved in randomization and study drug supply) will be blinded to study drug treatment until the 6-month treatment period data is unblinded for the primary analysis. Sponsor personnel who may have treatment assignment information will not have access to patient level data from the clinical trial database.

Purpose: Specify to 2 decimals the threshold for urinary oxalate excretion in the inclusion criteria and throughout the protocol.

The primary change occurs in Section 4.1, Inclusion Criteria #3

Now reads: Mean 24-hour urinary oxalate excretion from the first 2 valid 24-hour urine collections is ~~≥0.7~~ **≥0.70** mmol/24h/1.73m^2

Sections also containing this change:

- Synopsis
- Section 1.2.2, Summary of Clinical Data with Lumasiran

- Section 3.1, Summary of Study Design
- Section 3.5, Method of Assigning Patients to Treatment Groups

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Purpose: Update the threshold for the glomerular filtration rate to <30 mL/min/1.73 m^2 in the exclusion criteria; elsewhere state that patients included in this study have eGFR ≥30 mL/min/1.73m^2.

The primary change occurs in Section 4.2, Exclusion Criteria #4

Now reads: Estimated GFR of ~~≤45~~ **<30** mL/min/1.73m^2 at screening (calculation will be based on the Modification of Diet in Renal Disease [MDRD] formula for patients ≥18 years of age and the Schwartz Bedside Formula for patients <18 years of age).

Sections containing this change:

- Synopsis
- Section1.3, Study Design Rationale
- Section 1.4, Dose Rationale

Purpose: Delete paragraph to accommodate those site pharmacies whose established policy does not support masking the syringe prior to transfer of the study drug from vial to syringe

The change occurs in 5.2.2, Dose and Administration

Deleted text: ~~To maintain the blind, the syringes will be masked prior to study drug withdrawal from the masked vial. A pharmacist, or other qualified healthcare professional, will withdraw study drug from the masked vial into the masked syringe. A full description of the blinding procedure is included in the Pharmacy Manual.~~

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

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

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

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

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

~~b.~~ **c. If an alternative cause is not found,** perform assessments per Table 6 and Table 9.

Purpose: Add that male patients may be required to use contraception (condom) in some countries, such as France, to comply with local requirements.

The change occurs in Section 5.5.1, Contraception

Now reads: For male patients, no contraception is required. However, ~~contraception use by men should be consistent~~ **use by males of contraception (condom) may be required in some countries, eg, France, in order to comply** with local ~~regulations~~ **requirements** as described in the corresponding patient informed consent forms.

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

The primary change occurs in 6, Study Assessments

Now reads: The schedules of study assessments is provided in Table 1, Table 2, Table 3, and Table 4**. Study assessments for pregnancy test (urine or serum), clinical lab assessments, urine collection, and DNA testing may be conducted at a location other than the study center by a home healthcare professional, where applicable country and local regulations and infrastructure allow.**

Purpose: Add that patients may be rescreened per investigator judgment and after consultation with the Medical Monitor.

The primary change occurs in 6.1.2, Rescreening

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

Purpose: Specify that pregnancy tests may be performed more frequently per local requirements.

The primary change occurs in 6.5.6.2, Pregnancy Testing

Section now reads: A serum pregnancy test will be performed at Screening or upon initiation of menarche, if applicable, and urine pregnancy tests will be performed thereafter per the Schedules of Assessments and any time pregnancy is suspected. More frequent pregnancy testing may be performed where required per local ~~regulations~~ **requirements**.

Sections also containing this change:

- Table 1, Schedule of Assessments – 6-Month Double-Blind Treatment Period and Blinded Treatment Extension (Screening through Month 9 Assessments)
- Table 2, Schedule of Assessments – Open Label Extension Period (After Month 9 through Year 5)

Purpose: Clarify that if the relationship between an AE and the study drug is at least reasonably possible, it is considered "related" to the study drug.

The change occurs in Section 6.5.7.1 Definitions, Relationship of the Adverse Event to Study Drug

Now reads: 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.**

Purpose: Update the description of the quality of life questionnaire.

The change occurs in 6.7, Quality of Life

Now reads: QOL assessments include the following:

- Kidney disease Quality of Life Questionnaire (KDQOL), specifically the ~~KDQOL-SF1.3 and~~ KDQOL-36 for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL), including the generic and ESRD modules **(parent and/or self-report versions)** [20] for patients <18 years of age at screening.
- EQ-5D, a standardized instrument consisting of a questionnaire and a visual analog scale pertaining to 5 dimensions ~~(mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)~~. Scoring of the questionnaire is based on ~~3~~ degrees of disability ~~(severe, moderate, or none)~~. Scoring of the visual analog scale 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.

The **EQ-5D-**5L ~~value set~~ **questionnaire** will be utilized in patients ≥18 years of age at screening, and the ~~5Y~~ **EQ-5D-Y questionnaire** ~~value set~~ will be utilized in patients <18 years of age at screening**, where available**.[21]

Purpose: Update the description of the analysis populations.

The change occurs in 7.2.1, Populations to be Analyzed

Now reads:

- Per-protocol (PP) Set: All randomized patients who received any amount of study drug, had baseline and at least one post-baseline 24-hour urinary oxalate, and did not experience any major protocol deviations that may impact the efficacy results within the 6-month double-blinded period. Patients will be analyzed according to the **randomized** treatment ~~actually received~~ **arms.**
- **All Lumasiran Treated Set: All patients who received any amount of lumasiran including patients who took lumasiran during the 6-month double-blinded period and patients who initially took placebo during the 6-month double-blinded period and then switched to lumasiran during the extension period.**

The primary population used to evaluate efficacy will be the Full Analysis Set~~. The~~ **for the** primary endpoint ~~will also be analyzed for the Per-protocol Set~~ **and secondary endpoints during the double-blind period**. Safety **during the double-blind period** will be analyzed using the Safety Analysis Set. **The** PK **A**~~a~~nalysis **Set will be used to evaluate the PK endpoints. The All Lumasiran Treated Set** will be ~~conducted in the PK Analysis Set~~ **used to summarize the long-term efficacy and safety of lumasiran**.

Purpose: Update how missing data are handled.

The change occurs in 7.2.3, Handling of Missing Data

Deleted text: ~~To assess the impact of missing data under more conservative assumptions, a pattern mixture model (PMM) based on missing not at random (MNAR) assumptions will be performed as a sensitivity analysis.~~

Purpose: Update the description of the primary endpoint.

The change occurs in 7.2.5.1, Primary Endpoint

Now reads: The primary endpoint is to compare the percent change from baseline to Month 6 in 24-hour urinary oxalate corrected for BSA between the treatment groups in the Full Analysis Set. The analysis will be performed using a mixed-effect **model for**

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repeated measures (MMRM) approach. The outcome variable is percent change from baseline in urinary oxalate corrected for BSA. The model includes baseline value as covariate and fixed effect terms including treatment arm and visit (Months ~~1, 2,~~ 3, 4, 5, 6). **The treatment estimates from this model will represent an average percent change from baseline of 24-hour urinary oxalate excretion across months 3 through 6 at which the treatment effect is expected to have reached steady state. Furthermore, given the variability of 24-hour urinary oxalate, averaging the values across these visits will yield stable treatment estimates.**

Baseline and Month 6 urinary oxalate values are planned to be collected in triplicate (minimum requirement of duplicate) and the calculated ~~mean~~ **median** of valid collections during each time period (visit) will be used in the analysis. BSA will be calculated using the Mosteller formula.

Purpose: Update the description of the secondary endpoint analyses.

The primary change occurs in 7.2.5.2, Secondary Endpoints

Now reads:

To control the overall type I error, **these** secondary endpoints will be tested in the following hierarchical order:

- Absolute change in 24-hour urinary oxalate corrected for BSA from baseline to Month 6
- Change in 24-hour urinary oxalate:creatinine ratio (value/ULN) from baseline to Month 6
- Proportion of patients with 24-hour urinary oxalate level **at or** below 1.5xULN ~~[ULN=0.46 mmol/24h/1.73m^2]~~ at Month 6
- Proportion of patients with 24-hour urinary oxalate level **at or** below ULN ~~[ULN=0.46 mmol/24h/1.73m^2]~~ at Month 6
- **Percent change in plasma oxalate from baseline to Month 6**
- **Absolute change in plasma oxalate from baseline to Month 6**

Continuous endpoints will be analyzed using an MMRM approach similar to the one described for the primary endpoint. ~~For b~~**B**inary endpoints~~,~~ **will be analyzed using the Cochran-Mantel-Haenszel test stratified by baseline urinary oxalate. The** odds ratio and the differences in proportions with corresponding 95% confidence will **also** be summarized.

~~Change in eGFR from baseline to Month~~ **Secondary endpoints assessed beyond Month** 6 will be summarized descriptively. **Change in eGFR over time will also be summarized descriptively.**

Purpose: Update the description of the pharmacodynamic analysis.

The change occurs in 7.2.6, Pharmacodynamic Analysis

Now reads: ~~Urinary oxalate and glycolate excretion, urinary oxalate: creatinine ratio, and plasma levels of oxalate and glycolate will be summarized over time descriptively by treatment arm.~~ **Analysis of the PD parameters are specified in Section 7.2.5.2. Any PD parameters not already prespecified for testing will be summarized descriptively.**

Purpose: Stipulate discontinuation criteria for the termination of the clinical trial or a clinical study site.

The change occurs in Section 8.1.6, Termination of the Clinical Study or Site Closure

Now reads: The Sponsor**, or designee,** reserves the right to terminate the study ~~for~~ **or a** clinical ~~or administrative reasons~~**study site** at any time. ~~If the site does~~ **Conditions that may warrant this action may include, but are** not ~~recruit at a reasonable rate, or if there is insufficient adherence~~ **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, ~~the study may be closed at that site.~~ **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~~/IRB~~ 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.

Purpose: Remove that an Institution or Investigator must wait 18 months to submit a publication once the primary manuscript has been published since the number of months varies per local requirements and this information is specified in the clinical trial agreement.

The change occurs in Section 8.3, Publication Policy

Deleted text: ~~A separate publication by Institution or Investigator may not be submitted for publication until after this primary manuscript is published, or following the period of 18 months after completion of the study at all centers.~~

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

These changes are not listed individually.

ALN-GO1-003 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 23 July 2018

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

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to provide additional clarification about the patient caregiver surveys specific to patients under the legal age of consent, and to make corrections to the Open Label Extension Period Schedule of Assessments, which was missing the Month 27 visit in Year 2 (Study Day 757 ±14 days). In addition, the visit schedule for the 12-lead electrocardiogram and renal ultrasound assessments through Year 5 in the Open Label Extension Period was corrected from annually to Month 36 and Month 48.

In the clinical laboratory assessments table, a correction was made to remove the immunogenicity (antidrug antibodies) assessment from the table, which was erroneously included in the original table.

Also, the nomenclature used in the protocol title was updated.

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

Table 1: Protocol Amendment 1 Detailed Summary of Changes

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

Purpose: Updated nomenclature used in the protocol title

The primary change occurs in the title page

Revised title: ILLUMINATE-A~~003~~: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study with an Extended Dosing Period to Evaluate the Efficacy and Safety of Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1

Section(s) also containing this change:

- Synopsis

Purpose: Added Month 27 visit to the Open Label Extension Period Schedule of Assessments, and corrected scheduled visits for 12-lead ECG and renal ultrasound assessments from annually to Month 36 and Month 48.

The primary change occurs in Table 2: Schedule of Assessments – Open Label Extension Period (After Month 9 through Year 5)

Purpose: Updated patient and caregiver experience survey information

The primary change occurs in Section 6.8, Patient and Caregiver Experience Surveys

Revised text:

The patient and caregiver experience survey**s** assess~~es~~ patients' experience living with PH1, including their experience with PH1 treatments, as well as the effect of PH1 on patients' caregivers. Th**ese**~~is~~ survey**s** will be completed at the time points specified in the Schedules of Assessment (Table 1 and Table 2) and **each** take~~s~~ approximately 10 minutes to complete.

For the **Patient Experience Survey**, ~~patient portion of the experience survey~~, patients ≥1**3**~~8~~ years of age at screening will complete the survey themselves if they are able. If the patient is unable to complete the **Patient Experience Survey** ~~survey~~ alone, their caregiver or site staff may complete the survey for the patient. If the patient is <1**3**~~8~~ 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**~~the patient section of the survey on behalf of the patient for as long as the patient remains <18 years of age~~. ~~For patients who reach the legal age of consent per local regulations 18 years of age during the study, caregivers will be encouraged to continue completing the patient section of the survey, but are not required to do so.~~ **Additionally, for patients under legal age of consent at the time of screening, their caregiver will also 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**.

~~For the Caregiver Experience Survey, caregivers will be asked to complete the survey at all time points~~

Section(s) also containing this change:

- Section 6.9, Patient and Caregiver Impact Questionnaire

Purpose: Updated patient and caregiver impact questionnaire details

The primary change occurs in Section 6.9, Patient and Caregiver Impact Questionnaire

Added text: 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. This ~~survey~~ **questionnaire** will be completed at the time points specified in the Schedules of Assessment (Table 1 and Table 2) and takes approximately 10-12 minutes to complete.

Patients ≥1**3**~~8~~ years of age at screening will complete the questionnaire themselves 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 <1**3**~~8~~ years of age at screening, a caregiver will complete the ~~patient section of the~~ questionnaire on behalf of the patient ~~for as long as the patient remains <18 years of age~~. For patients who reach **the legal age of consent per local regulations** ~~18 years of age~~ 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

Section(s) also containing this change:

- Section 6.8, Patient and Caregiver Experience Surveys

Purpose: Correct typographical errors, punctuation, grammar, abbreviations, and formatting

These changes are not listed individually.