Official Title: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, PHARMACODYNAMICS, ANDPHARMACOKINETICS OF LUMASIRAN IN PATIENTS WITH RECURRENT CALCIUM OXALATE KIDNEY STONE DISEASE AND ELEVATED URINARY OXALATE LEVELS**

NCT Number: **NCT05161936**

Document Date: **Protocol, Version 2.0, 07 July 2022**

CLINICAL STUDY PROTOCOL
ALN-GO1-008
DATED 07 JULY 2022

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Short Title:	A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2021-001519-10
IND Number:	128941
Protocol Date:	Original protocol, 24 June 2021 Amendment 1, 16 June 2022 Amendment 2, 07 July 2022
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

08-Jul-2022 | 9:15 PM EDT

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-008 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Short Title

A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Study Drug

Lumasiran (ALN-GO1)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 55 clinical study centers worldwide including in Europe and North America.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event

Objectives	Endpoints
• To evaluate additional pharmacodynamic (PD) parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize the pharmacokinetics (PK) of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of adverse events (AEs)

Study Design

This is a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered subcutaneously (SC) in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1).

Number of Planned Patients

The planned enrollment for this study is 120 patients.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years of age) with a documented diagnosis of recurrent kidney stone disease based on ≥2 stone events, with a minimum of 1 stone event within the 5 years prior to screening. A historical kidney stone event is defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on computed tomography (CT) imaging
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Study Drug, Dose, and Mode of Administration

Lumasiran (ALN-GO1) is a SC administered *N*-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA) targeting liver-expressed hydroxyacid oxidase (*HAO1*) messenger RNA (mRNA) for reduction of hepatic oxalate production.

Lumasiran will be administered by SC injection at a dose of 284 mg or 567 mg on Day 1, Month 3, and Month 9.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered at the same dosing interval as lumasiran.

Duration of Treatment and Study Participation

The duration of treatment with study drug is up to 15 months. The estimated total time on study for each patient is up to 17 months, including up to 2 months of screening.

Statistical Methods

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05.

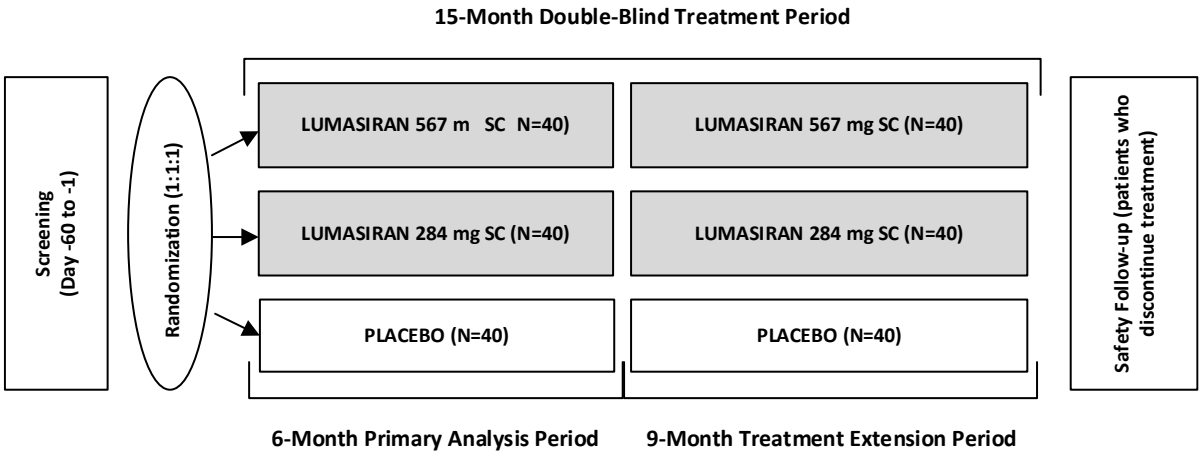
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients who received at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Plasma Oxalate Analysis Set:** All patients who received at least 1 dose of study drug and have a baseline plasma oxalate level ≥1.5 times the lower limit of quantification/detection.
- **Safety Analysis Set:** All randomized patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.
- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary efficacy endpoint will be analyzed in the FAS using a mixed-effect model for repeated measures (MMRM) approach. The primary comparison is percent change from baseline in urinary oxalate through Month 6.

Safety data will be summarized descriptively.

Figure 1: Study Design



Abbreviations: SC=subcutaneous(ly)

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]							Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period		
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Informed consent	Section 6.1	X								
Assign patient identification number	Section 3.4	X								
Demographics	Section 6.1	X								
Blood for DNA analysis	Unless tested previously, see Section 6.1.1	X								
Full physical examination	Section 6.5.3	X							X	
Follicle-stimulating hormone	To confirm postmenopausal status if applicable; Section 6.5.4.2	X								
Serum pregnancy test (for WOCBP)	See Section 6.5.4.2	X								

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]							Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period		
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
2 separate 24-hour urine collections	2 valid screening collections (see Section 6.2.1.1); an additional collection may be required (see Section 6.2.1.1) Collect within 14 days prior to dosing (M9) or visit (M15); repeat if invalid. See Table 4	X						X	X	
Inclusion/exclusion criteria	Section 4.1; Section 4.2	X	X[b]							
Medical history	Section 6.1	X	X							
Height	Section 6.5.2	X	X						X	
Vital signs	Section 6.5.1	X	X	X				X	X	X
Body weight	Section 6.5.2	X	X	X				X	X	X
Patient Diary	Diet compliance check and 24-hour urine collection; Section 5.6.3	X		X	X	X	X	X	X	

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]							Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period		
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Single 24-hour urine collection	Collect within 14 days prior to dosing (M3) or visit (M4, M5, M6); repeat if invalid. See Table 4			X	X	X	X			
Blood sample for PD analyses	Section 6.3	X	X	X			X	X	X	
Clinical laboratory assessments	Section 6.5.4	X	X	X			X	X	X	X
Antidrug antibody sample	Section 6.5.4.1		X	X			X	X	X	X
Urine pregnancy test (for WOCBP)[c]	May be performed more frequently where required per local requirements, or if pregnancy is suspected. See Section 6.5.4.2		X	X				X		
Symptom-directed physical examination	Section 6.5.3		X	X				X		X
Prior and concomitant medications	Section 5.4	Continuous								

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]							Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period		
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Clinical kidney stone events	Section 6.2.2	Continuous								
Review/record adverse events	Section 6.5.5	Continuous								
Healthcare utilization	Section 6.6	Continuous								
Randomization	Window: 1 business day prior to Day 1 for study drug preparation		X							
Blood samples for PK analyses	Table 2; Section 6.4		X							
Study drug administration	Section 5.2.2		X	X				X		
Optional low-dose kidney-protocol CT scan[d]	Section 6.2.2.2		X (-3 days window)						X	

Abbreviations: CT=computed tomography; D/C=discontinue; ET=early termination; EOS=end of study; EOT=end of treatment; M=month; PD=pharmacodynamic; PK=pharmacokinetic; WOCBP=women of child-bearing potential

Notes:

- When scheduled at the same time points, assessments of vital signs should be performed before physical examinations and blood sample collections, where feasible.
- Patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses (refer to Section 4.3.1).

- White columns indicate visits to the clinical study center; gray-shaded columns indicate study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion and with oversight of the Investigator, based on safety and tolerability), provided (for dosing visits) that the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a symptom-directed physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, kidney stone events, and adverse events.

Footnotes:

[a] **All assessments are required to be performed prior to dosing at dosing visits, except for the PK 2-hour postdose sample collection and optional CT scan.**

[b] Inclusion/exclusion criteria should be verified prior to randomization. Laboratory assessments conducted to confirm study eligibility will not be repeated unless the time between screening and randomization exceeds 4 weeks.

[c] Pregnancy test results must be known prior to dosing, if applicable.

[d] Patients who elect to participate in optional CT scans will be requested to complete CT scans at both baseline (may be performed up to 3 days prior to Day 1), and at Month 15. The CT scans may be performed after dosing, if required.

Table 2: Pharmacokinetic Time Points

Study Day	Sampling Time (hh:mm)	Blood PK Sample
Day 1	Predose (any time before dosing)	X
	02:00 (±30 min)	X

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

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 7.2.7 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum plasma concentration
CPC	Clinical product complaint
CT	Computed tomography
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
ESKD	End stage kidney disease
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
GO	Glycolate oxidase
HAO1	Hydroxyacid oxidase 1
HED	Human equivalent dose
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamics
PH1/2/3	Primary hyperoxaluria type 1/2/3
PK	Pharmacokinetic
PT	Preferred term
RNAi	Ribonucleic acid interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) has developed 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*) messenger ribonucleic acid (mRNA), blocking production of glycolate oxidase (GO) and hence reducing hepatic oxalate production.

Lumasiran is approved for the treatment of primary hyperoxaluria type 1 (PH1) in both pediatric and adult patients in the United States (23 November 2020) and in the European Union (19 November 2020). Based on lumasiran's mechanism of action, and demonstrated reduction of hepatic oxalate production in patients with PH1, the Sponsor is investigating whether treatment with lumasiran is effective for patients with recurrent calcium oxalate kidney stone disease who have elevated urinary oxalate levels but have not been diagnosed with PH1 or one of the other primary hyperoxalurias.

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

1.1. Study Rationale

Study ALN-GO1-008 is a randomized, double-blind, placebo-controlled, multi-center Phase 2 study designed to evaluate the efficacy, safety, pharmacodynamics (PD), and pharmacokinetics (PK) of lumasiran, administered subcutaneously (SC), in adult patients with recurrent calcium oxalate kidney stone disease.

The primary objective of the study is to evaluate the effect of lumasiran on the percent change in urinary oxalate excretion in patients with recurrent calcium oxalate kidney stones. Secondary and exploratory objectives of the study include the evaluation of the effect of lumasiran on urinary calcium oxalate supersaturation, the occurrence of kidney stones, the PD effect of lumasiran on plasma oxalate, plasma glycolate and urinary glycolate, and the characterization of plasma PK.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Kidney stones are common, affecting approximately 1 in 11 people in the United States, and the prevalence of kidney stone disease has been increasing worldwide over time.[Scales 2012] Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals, with the remainder being predominantly calcium phosphate, uric acid, cystine, or struvite.[Worcester and Coe 2008; Worcester and Coe 2010] Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine (Figure 2). High levels of urinary oxalate may be derived from both endogenous synthesis and diet.

Kidney stones can develop in patients of all ages; however, the highest incidence rates occur in individuals aged 40 to 66 years.[Shin 2018] There is significant clinical burden associated with the development of kidney stones for patients with recurrent calcium oxalate kidney stone disease, including pain, infection/sepsis, diagnostic and therapeutic procedures, hospitalizations,

and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease (ESKD).

The typical clinical presentation of kidney stones includes sudden onset of lumbar flank pain and hematuria, and may include nausea and vomiting. Evaluation to assess etiology includes assessment of the patient's medical history, medication use, and dietary and lifestyle risk factors. Confirmation of diagnosis may involve renal ultrasound, abdominal x-ray, and/or computed tomography (CT).[Heilberg and Schor 2006] 24-hour urine collections analyzed for total volume, calcium, oxalate, uric acid, citrate, and other analytes may help to determine the underlying etiology.[Pearle 2014] Stone composition is generally determined in at least one instance.

There are limited effective treatment options for patients with recurrent calcium oxalate kidney stone disease. Preventive measures in American and European guidelines recommend adequate fluid intake to ensure a urine volume of at least 2 to 2.5 liters daily and provide dietary advice to limit the consumption of oxalate-rich foods, sodium chloride, and animal protein content, while maintaining a normal calcium intake. In some situations, thiazide diuretics, potassium citrate, and/or allopurinol may be considered.[Pearle 2014; Türk 2021]

Treatment of pain associated with kidney stone events may involve non-steroidal anti-inflammatory agents and/or opiate pain medications. Depending on the clinical context, medical expulsive therapy, extracorporeal shock-wave lithotripsy, ureteroscopy, stenting, and percutaneous nephrolithotomy are some of the treatment options that may be pursued.[Türk 2021]

Lumasiran is a ribonucleic acid interference (RNAi) therapeutic designed to reduce hepatic oxalate production. Oxalate produced by the liver is largely excreted in the urine, and lumasiran has been shown to reduce urinary oxalate in patients with PH1. High levels of urinary oxalate increase the risk of stone formation; therefore, lumasiran may have efficacy in patients with recurrent calcium oxalate kidney stone disease who do not have PH1 but who produce high amounts of oxalate endogenously.

1.3. Benefit-Risk Assessment

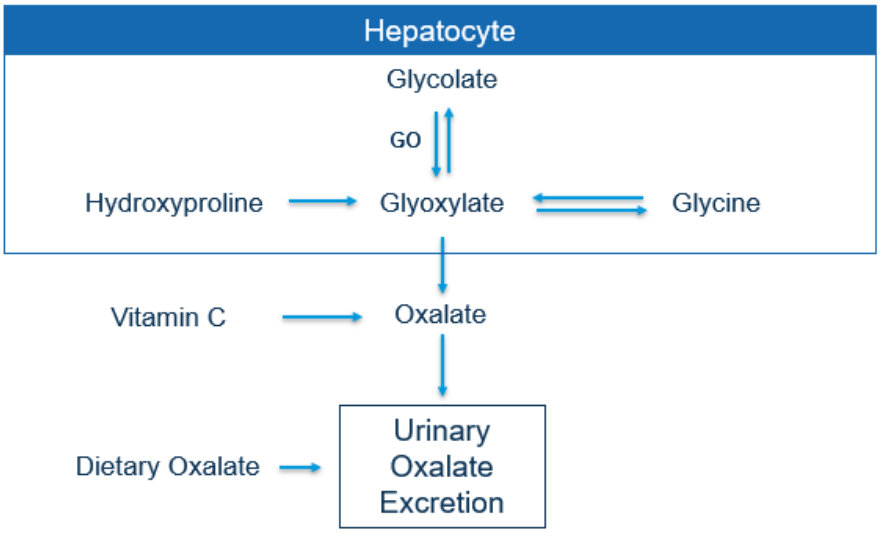
Calcium oxalate stone formation occurs when a supersaturating level of calcium oxalate is present in the urine, with increasing risk of stone formation as urine oxalate levels increase.[Curhan and Taylor 2008] More than half of oxalate is endogenous in origin and presumed to come largely from the liver.[Mitchell 2018] Studies have shown that reduced calcium oxalate supersaturation and urinary oxalate levels are associated with reduced stone formation.[Borghi 2002; Ferraro 2018; Prochaska 2018]

For patients with recurrent calcium oxalate stone formation, multiple stone removal procedures may be required. These procedures are invasive and place the patient at risk of complications including bleeding and infection. Patients experiencing obstructive kidney stones can also experience acute kidney injury with permanent loss of renal function. As a result, patients with recurrent kidney stone formation have a higher risk of progression to CKD and ESKD.[Dhondup 2018; Rule 2009]

Lumasiran, approved in the United States and European Union for the treatment of PH1, is designed to reduce hepatic production of oxalate. Based on the available data from clinical and

nonclinical studies, lumasiran, administered SC, demonstrated a potent, dose-dependent inhibition of GO resulting in decreased urinary and plasma oxalate and increased plasma and urinary glycolate. Lumasiran may be effective in lowering urinary oxalate levels in patients with recurrent calcium oxalate kidney stone disease (Figure 2). No adverse effects of elevated glycolate have been reported. Unlike oxalate, glycolate is highly soluble and readily excreted in the urine.

Figure 2: Summary of Endogenous Oxalate Synthesis



Abbreviations: GO=glycolate oxidase

Lumasiran has been well tolerated with an acceptable safety profile in studies with healthy volunteers and patients with PH1. Most adverse events (AEs) have been mild or moderate in severity. Transient, mild injection site reactions (ISRs) have been observed. No clinically significant laboratory changes related to lumasiran 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 hepatic effects. The study has specific 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 (LFTs). As the risk of embryofetal toxicity in humans is currently unknown, females who are of child-bearing potential during the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use contraception as specified in the protocol (see Section 5.6.1).

Based on the available efficacy and safety data from clinical and nonclinical studies, the benefit-risk assessment supports the evaluation of lumasiran in a Phase 2 study in patients with recurrent calcium oxalate kidney stone disease.

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

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event
• To evaluate additional PD parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize PK of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6

Objectives	Endpoints
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of AEs

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered SC in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

The study will consist of up to 2 months of screening and 15 months of double-blind treatment (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period). Patients will be screened from Day -60 to Day -1 to determine eligibility. During screening, patients will provide at least two 24-hour urine collections to establish baseline urinary oxalate levels. Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1), as discussed in Section 3.4.

During the 6-month Primary Analysis Period, patients will be dosed on Day 1 (baseline) and at Month 3. During the Treatment Extension Period, one additional dose will be administered at Month 9; an end of study (EOS) visit will take place at Month 15. Study drug will be administered SC as specified in Section 5.2.2. Patients will be assessed for efficacy, safety, PD, and PK according to the Schedule of Assessments (Table 1 and Table 2). Efficacy assessments will include evaluation of urinary oxalate excretion, urinary calcium oxalate supersaturation, and kidney stone events (including clinical events and radiologic events with optional low-dose kidney-protocol CT). Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, physical examinations, and concomitant medications.

Patients who discontinue study drug early will be asked to return for follow-up visits as described in Section 4.3.1.

3.2. Scientific Rationale for Study Design

The primary endpoint for this Phase 2 study is the percent change in 24-hour urinary oxalate excretion. To confirm the optimal dosing regimen, and to facilitate the collection of kidney

stone event data (an exploratory endpoint), the study will continue through Month 15. A placebo comparator is included because there is no approved standard of care therapy to decrease urinary oxalate.

A blood DNA sample will be collected as part of standard screening assessments (if testing has not already been performed) to ensure the exclusion of patients with primary hyperoxaluria type 1 (PH1), type 2 (PH2), and type 3 (PH3). Lumasiran is approved in some countries for the treatment of PH1, and patients with PH2 and PH3 are not expected to respond to lumasiran.

Because the primary endpoint will rely on measurements of urinary oxalate, and because some urinary oxalate is diet-derived, diet is an important variable in this study. In a 5-year study of recurrent stone formers published by Borghi et al, patients randomized to a normal calcium, low protein/salt diet had lower urinary oxalate levels and a lower cumulative incidence of recurrent kidney stones when compared to a low calcium diet. During the current study, and as of the time of informed consent, patients will be asked to adhere to a diet appropriate for stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate.

The secondary endpoint to assess meaningful reduction in 24-hour urinary oxalate from baseline to Month 6 (Months 4 through 6) defines a clinically meaningful reduction as ≥20% in the non-PH1 stone former population, supported by available literature based on stone former populations.[Borghi 2002]

In this study, lumasiran will be evaluated in patients with recurrent calcium oxalate kidney stone disease. Due to the limited and burdensome disease management options, there is an unmet need for new therapies.

3.3. Justification for Dose

Two dose levels of lumasiran 284 and 567 mg given on Day 1, Month 3, and Month 9 were selected to evaluate urinary oxalate dose response. The higher dose level of 567 mg is expected to suppress GO enzyme by ≥95%, comparable to the regimen evaluated in ALN-GO1-003 (ILLUMINATE-A) in patients with PH1. The lower dose of 284 mg is expected to suppress GO enzyme by 90%. In addition, the fixed doses will simplify dose administration in this adult study population. Both regimens are predicted to achieve near-steady state ribonucleic acid-induced silencing complex (RISC) concentrations and urinary oxalate suppression at Month 6. Month 9 dosing is intended to sustain PD effect through Month 15 and will provide data to differentiate the effect of every 3 months and every 6 months dosing on urinary oxalate reduction.

Single 0.3 to 6.0 mg/kg doses of lumasiran in healthy subjects and multiple 3.0 mg/kg doses of lumasiran administered monthly or once every 3 months in patients with PH1 have been well tolerated. Plasma and liver exposure for the lumasiran 284 and 567 mg doses are expected to be in the range of 3.0 to 6.0 mg/kg lumasiran doses evaluated in healthy subjects in ALN-GO1-001 (Part A) and patients with PH1 in ALN-GO1-001 (Part B), ALN-GO1-002, and ILLUMINATE-A. Based on rat and monkey NOAEL doses of lumasiran 200 mg/kg and 300 mg/kg, a sufficient safety margin exists for the use of lumasiran 284 and 567 mg doses (refer to the ALN-GO1 Investigator Brochure).

Based on a 70 kg patient, the planned doses of 284 mg and 567 mg equate to approximately 4.0 mg/kg or 8.0 mg/kg, respectively. The human equivalent dose (HED) margin values for the

approximate 4 mg/kg clinical dose were 8.1-fold for the chronic rat study and 24.2-fold for the chronic monkey study; the HED margin values for the approximate 8.0 mg/kg clinical dose were 4.0-fold for the chronic rat study and 12.1-fold for the chronic monkey study (refer to the ALN-GO1 Investigator Brochure).

3.4. Method of Assigning Patients to Treatment Groups

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. After the patient signs the informed consent form (ICF) and before proceeding with screening procedures, the Investigator or his/her designee will contact the Interactive Response Technology (IRT) to obtain a patient identification number.

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

Patients will be randomized 1:1:1 to receive lumasiran 284 mg, lumasiran 567 mg, or placebo, administered at the same volume (see Section 5.2.2), for the duration of the study. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1).

For stratification, the number of historical kidney stone events occurring in the 12 months prior to screening are considered, and defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 12 months prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

3.5. Blinding

Site personnel and patients will be blinded to study drug treatment; site personnel preparing study drug may be unblinded to study drug treatment only where required by documented institutional procedure. The Sponsor will have access to unblinded study data during the conduct of the study. Lumasiran and placebo will be packaged identically and will be administered at the same volume under the supervision of the Investigator at the study center or by a healthcare professional at the patient's home (see Section 5.2.2). Since lumasiran may be visually

distinguishable from placebo, the syringe will be masked prior to administration by a healthcare professional. See the Pharmacy Manual for additional details.

All site personnel will be blinded to laboratory results of oxalate, calcium oxalate supersaturation, and glycolate from after the time of the first dose until unblinding. Results will not be reported to the Investigator from the first dose until the last patient completes assessments at the Month 15 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 measurements for oxalate, calcium oxalate supersaturation, or glycolate from the first dose until the sites and patients are unblinded, or until the patient ends the study, whichever is earlier. If oxalate, calcium oxalate supersaturation, or glycolate are 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.

Any unplanned unblinding occurring during the study period will be documented and reported in the clinical study report.

3.5.1. 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. If contact prior to unblinding is not possible, personnel must contact the Medical Monitor 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 trial master file.

Refer to the IRT instructions for details on unblinding.

3.6. Safety Review

A safety review committee will not be utilized for this study; however, the Sponsor will monitor safety on an ongoing basis and in accordance with the Sponsor's internal processes.

3.7. Definition of End of Study for an Individual Patient

A patient is considered to have reached the EOS if the patient:

- has completed the EOS (Month 15) visit, or
- has completed safety monitoring following the final dose of study drug as described in Section 4.3.1

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

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

Age

1. Age 18 years or older (or age of legal consent, whichever is older).

Patient and Disease Characteristics

2. Recurrent kidney stone disease, defined as ≥2 stone events, with a minimum of 1 stone event within the 5 years prior to screening. For inclusion, a historical kidney stone event is defined as:
   - the visible passage of a kidney stone
   - a procedural intervention for removal of an asymptomatic or symptomatic stone
     - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
     - if more than 1 procedure was required to remove a single stone, this counts as 1 event
   - a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
     - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.
3. The 2 most recently analyzed kidney stones prior to randomization contained 50% or more of calcium oxalate; if only one stone analysis is available, then it must have contained 50% or more of calcium oxalate.
4. 24-hour urinary oxalate levels from 2 valid 24-hour urine collections obtained during screening are >ULN (ULN = 40 mg/24 hours).
5. Willing to adhere to dietary recommendations appropriate for stone formers including limiting vitamin C supplementation to <200 mg daily.
6. If taking medications and/or hydrating for kidney stone prophylaxis, or taking medications that alter urinary oxalate excretion and/or kidney stone formation, must have been on a stable regimen for at least 60 days before randomization, and willing to remain on this stable regimen for the duration of the study.
7. Body mass index (the weight in kilograms divided by the square of the height in meters) at screening of 20 to <40 kg/m^2.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

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

Laboratory Assessments

1. Has any of the following laboratory parameter assessments at screening:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN
    b. Total bilirubin >1.5 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
2. Has an eGFR of <30 mL/min/1.73m^2 at screening (calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine formula; see Section 10.1).

Prior/Concomitant Therapy

3. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.

Medical Conditions

4. Patients with a known history of secondary causes of elevated urinary oxalate and/or recurrent kidney stones including:
    a. Primary hyperoxaluria
    b. Severe eating disorders (anorexia or bulimia)
    c. Chronic inflammatory bowel disease
    d. Intestinal surgery with malabsorption or chronic diarrhea
    e. Sarcoidosis
    f. Primary hyperparathyroidism
    g. Complete distal renal tubular acidosis
5. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
6. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
7. History of intolerance to SC injection(s).

Contraception, Pregnancy, and Breastfeeding

8. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.6.1.
9. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol Use

10. 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]).
11. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.

4.3. Removal from Study Drug or Assessment

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

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

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

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

- Significant protocol deviation
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.5.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

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

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of

the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including serious adverse events (SAEs), the event should be followed as described in Section 6.5.5. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month Primary Analysis Period (defined as a discontinuation that occurs after the first dose of study drug administration on Day 1 during the 6-month Primary Analysis Period) will be encouraged to remain on the study and complete all assessments (including 24-hour urine collections) through Month 6, with early termination (ET) assessments at Month 9, and safety follow-up per the safety follow-up schedule (Table 1). Patients who do not remain on the study through Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete safety follow-up per the safety follow-up schedule (Table 1).

Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete a safety follow-up visit per the safety follow-up schedule (see Table 1).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the ET assessments (see Table 1).

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

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

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

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

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

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments through the Primary Analysis Period (Month 6).

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

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

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.5.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient 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 continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (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.

- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

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

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug (lumasiran and placebo) 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 study drug 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

Patients will be administered SC injections of lumasiran (284 mg or 567 mg) and/or placebo at the same volume, as described below, on Day 1, Month 3, and Month 9.

Lumasiran 567 mg	**Lumasiran 284 mg**	**Placebo**
1.5 mL lumasiran 1.5 mL lumasiran	1.5 mL lumasiran 1.5 mL placebo	1.5 mL placebo 1.5 mL placebo

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, syringes are to be masked prior to the removal of study drug from vials. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be permitted at a location other than the study center (for example, the patient's home) by a healthcare professional with the oversight of the Investigator, provided the patient has tolerated at least 1 dose of study drug administered in the clinic. However, continued study

drug administration at the study center should be considered for patients who have ongoing study drug-related AEs 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 visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.5.8.

5.2.3. Dose Modifications

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. Results of previous LFT assessment 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 3.
3. For any ALT or AST elevation >3× ULN:
    a. If local laboratory results are obtained, confirm with a 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 5 and Table 6.
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 3.

Table 3: 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least every 2 weeks: LFT per Table 5 • 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 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. • Evaluate the initial elevation in LFT per the following assessments until satisfactory resolution: – Table 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; 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. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically non-medical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For CPCs, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. Clinical product complaints that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.5. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Concomitant Medications and Procedures

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

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

Standard vitamins and topical medications are permitted (vitamin C supplementation must be <200 mg daily per inclusion criteria). However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

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.

5.5. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.6. Other Requirements

5.6.1. Contraception

Females of child-bearing potential must be willing to use an acceptable method of contraception from 14 days before first dose, throughout study participation, and for 6 months after last dose administration or until study completion.

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 (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and for up to 6 months after the last dose of study drug.

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

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral oophorectomy, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by a 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, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.4.2).

5.6.2. 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.

5.6.3. Dietary Restrictions

For the duration of the study patients should adhere to a diet appropriate for calcium oxalate stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate. Details are provided in the Dietary Reference Sheet.

Dietary adherence will be collected in a patient diary at the time points listed in the Schedule of Assessments (Table 1). Refer to the Study Manual for more information.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1. All assessments are required to be performed prior to dosing at dosing visits, except for PK 2-hour postdose sample collection and optional CT scans. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, and as noted in Table 1, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include pregnancy testing (urine or serum), clinical laboratory assessments, urine collections, DNA testing, symptom-directed physical examination / body system assessment, vital signs, body weight, height, blood collection for PD and ADA analyses (at the discretion and with oversight of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient before the screening procedures are initiated. All patients will be given a signed and dated version of their ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. To confirm study entrance criteria, 24-hour urine will be collected per Table 4.

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and prior to dosing will be updated.

6.1.1. DNA Sample

A blood sample for DNA analysis will be collected from all patients as part of the screening assessments. The samples will be analyzed for PH1, PH2, and PH3 (unless tested previously) to confirm eligibility (see Section 4.2). Refer to the Laboratory Manual for more information.

6.1.2. Retesting

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

6.1.3. Rescreening

Rescreening of patients is permitted with approval of the Medical Monitor. 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 be allowed to return for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment with study drug. The site should update the patient's status in the IRT to reflect this as soon as possible.

6.2. Efficacy Assessments

Efficacy assessments are to be performed as specified in the Schedule of Assessments (Table 1).

6.2.1. 24-Hour Urine Collections

Urinary oxalate excretion and calcium oxalate supersaturation (calculated from multiple parameters) will be determined from 24-hour urine sample collections to be completed at the time points specified in the Schedule of Assessment (Table 1). The start and stop dates/times of collection, the volume of urine in the collection, whether there were any missed voids, and whether the patient complied with dietary recommendations will be recorded. An aliquot of the 24-hour urine collection will also be used to determine urinary creatinine content and to determine if the 24-hour urine collections need to be repeated (see Section 6.2.1.1).

The 24-hour urine collection procedure by study visit is provided in Table 4.

Table 4: 24-hour Urine Collection Procedure by Study Visit

Study Visit and Urine Collection Window	**Number of Collections to Schedule**	**Validity Requirement Prior to Dosing/Visit** (see Section 6.2.1.1)	**Notes**
Screening (within 60-day period)	2	2 valid collections prior to dosing unless variability criterion is not met (Section 6.2.1.2), in which case an additional collection is required[a].	Supervised collections[b] are encouraged unless patient is already familiar with the collection procedure. If any collections are invalid, the remaining collections for screening must be supervised.
Months 3, 4, 5, and 6 (within 14 days prior to dosing/visit)	1	No	If an invalid collection is obtained for the timepoint, a single repeat collection must be supervised. Repeat collection, if necessary, is to be completed within ±14 days of dosing/visit.
Months 9 and 15 (within 14 days prior to dosing/visit)	2	1 valid collection prior to dosing/visit	If a patient has had ≥2 prior invalid collections, both collections at these visits must be supervised[b]. At least 1 valid collection must be obtained prior to dosing/visit. If any collections for the timepoint are invalid, the remaining collection(s) for the timepoint must be supervised.

[a] The additional collection is not required to be valid in order to proceed with dosing, but will be tested to confirm validity for the calculation of baseline 24-hour urinary oxalate.

[b] A supervised collection is defined, at a minimum, as contact from study staff to the patient the day prior to the collection start and the day the collection will finish to ensure compliance; this may be conducted remotely. Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine collection is not a supervised collection, or if a collection is supervised remotely, patients may either bring it to the clinic or have it couriered to the clinic.

6.2.1.1. Validity Criteria for 24-hour Urine Collections

Throughout the study, a urine collection will be considered valid if each of the following criteria are met:

- The collection is between 22 to 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.
- Patient complied with dietary recommendations appropriate for oxalate stone formers (detailed in the Dietary Reference Sheet) for the 4 days prior to the start of the urine collection and during the collection.

24-hour urine collections that are known to be invalid should still be submitted for analysis.

6.2.1.2. Variability Criterion for 24-hour Urine Collections at Screening

If the 2 valid 24-hour urine collections from screening meet eligibility requirements (both 24-hour urinary oxalate levels >ULN), the variability between the oxalate levels (in mg/day) should be assessed as follows:

$$Variability = \left|\frac{(Oxalate\ value\ \#1 - Oxalate\ value\ \#2)}{(Average\ of\ oxalate\ values\ \#1\ \&\ \#2)}\right| \times 100\%$$

If the variability is >20%, then an additional 24-hour urine collection should be obtained. The result of the additional sample will not impact the patient's eligibility for the study.

6.2.2. Kidney Stone Events

Since kidney stone events are recorded as an efficacy assessment, these events will not be captured as AEs or SAEs. However, if a patient experiences other AEs or SAEs during a kidney stone event, they should be reported as an AE (see Section 6.5.5.2).

Kidney stone events will be graded by the Investigator as mild, moderate, or severe as defined in Section 6.5.5.1. If there are changes in grade during an event, only the highest grade should be reported.

6.2.2.1. Clinical

All relevant clinical information pertaining to kidney stone events should be obtained, including laboratory values, medical records, discharge summaries, and medical test results (including stone composition, if available, and radiology reports). A clinical kidney stone event is defined as one of the following:

- Visible passage of a kidney stone
- A procedural intervention for removal of an asymptomatic or symptomatic stone (information on the location, number, and size of stones removed will be collected)

- Or, in the case of potential stone passages without visible stones, it will be up to the Investigator to evaluate patients' symptoms and determine whether a stone passage occurred or the symptoms were due to a different cause.

6.2.2.2. Radiographic

For patients who elect to participate in optional CT scans, a non-contrast low-dose kidney-protocol CT scan will be performed at baseline (may be performed up to 3 days prior to Day 1), and at Month 15.

For patients who elect to participate in optional CT scans and terminate the study early, a CT scan should be performed at the ET visit only if this visit occurs after Month 6 and at the discretion of the Investigator, and where permitted, following consultation with the Medical Monitor. Optional CT scans will be analyzed centrally.

6.2.3. Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR (mL/min/1.73m^2) will be obtained at the time points specified in the Schedule of Assessment (Table 1).

eGFR will be calculated based on the CKD-EPI formula (see Section 10.1).[Levey 2009; Schwartz 2009]

6.3. Pharmacodynamic Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma oxalate and plasma glycolate, and 24-hour urinary glycolate) at the time points specified in the Schedule of Assessments (Table 1). On dosing days, all blood and urine samples will be collected prior to study drug administration.

All PD assessments will be analyzed centrally. Postdose PD results will not be distributed to the sites until after the last patient completes assessments at the Month 15 visit. Site personnel should refrain from obtaining or viewing local oxalate, calcium oxalate supersaturation, or glycolate assessments, except as medically indicated, due to risk of unblinding (Section 3.5). Details regarding the processing and aliquoting of PD samples for shipping and storage are provided in the Laboratory Manual.

Where local regulations allow and infrastructure is in place, a healthcare professional may collect urine or blood samples offsite.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of lumasiran PK parameters at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

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

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded as either medical history or AEs, as appropriate.

Safety assessments are to be performed as specified in the Schedule of Assessments (Table 1). On dosing days and as applicable, assessments of vital signs, weight/height, physical examination, and clinical laboratory assessments are to be completed before study drug administration.

Adverse event assessments are detailed under Section 6.5.5.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. 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 predose in the seated or supine position, after the patient has rested comfortably for approximately 5 minutes. Blood pressure should be taken using the same arm when feasible. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

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

Vital signs results will be recorded in the eCRF.

6.5.2. Height and Weight

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); 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. If a visit is conducted offsite (eg, home), a body system assessment may be performed in lieu of a physical examination.

Symptom-directed physical examinations will be guided by evaluation of ongoing symptoms, changes in symptoms, or the onset of new symptoms, since the last visit. If there are no ongoing symptoms, changes in symptoms, or new symptoms, then a symptom-directed physical examination is not required.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history eCRF (if observed during screening) or the AE eCRF (if observed at any post-screening visit).

6.5.4. 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. Laboratory assessments conducted to confirm study eligibility (Section 4) will not be repeated unless the time between screening and randomization exceeds 4 weeks. 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, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and included in the clinical database. Clinical laboratory assessments are listed in Table 5 and will be assessed as specified in the Schedule of Assessments (see Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of visit assessments, all laboratory assessments specified in Table 5 which are performed at a local laboratory should also be sent in parallel to the central laboratory. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results on samples drawn on the same day.

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 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR[a]	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation	
International Normalized Ratio (screening only)	
Immunogenicity (see Section 6.5.4.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.4.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone
[a] Refer to Section 10.1 and the laboratory manual for further instructions on calculating eGFR.

6.5.4.1. Immunogenicity

Blood samples will be collected to evaluate ADA. Blood samples for ADA testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1).

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

6.5.4.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed thereafter per the Schedule 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 that is 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 6.5.5.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal. Postmenopausal women and women who are permanently sterilized will not undergo pregnancy testing.

6.5.4.3. 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 (see Table 3). Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments per Table 3, and other assessments or evaluations per Investigator discretion, as appropriate.

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

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

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

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

Note:

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

6.5.5. Adverse Events

6.5.5.1. Definitions

Adverse Event

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

Serious Adverse Event

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

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

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3× ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or ISRs 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 6.5.5.2 and Section 6.5.5.3, 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 AE.

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

Adverse event 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.

6.5.5.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient 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, 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 EOS. Non-serious AEs will be followed until the EOS. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the EOS. Serious AEs 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 the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to eCRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

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

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

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), 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 eCRF 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).

6.5.5.4. 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 6.5.5.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious

- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious AEs 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.

6.5.5.5. 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.

6.5.5.6. 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.

6.5.5.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 6 months following the last dose of study drug, 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 6 months 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 6.5.5.4.

The reporting of any pregnancy outcome for a female partner of a male patient participating in this study that results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly should be reported to the Investigator, who will then report this to the Sponsor or designee. The pregnancy outcome is to be recorded on the pregnancy reporting form.

6.5.5.8. Reporting of Overdose and Other Special Situations

An overdose is defined as any dose of study drug administered to the participant that is ≥2-fold the assigned dose during a single administration.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs. Overdose per se will not be categorized as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported as an SAE regardless of sequelae.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Healthcare Utilization

To complement medical records, information regarding health resource use related to kidney stone events will be collected as specified in the Schedule of Assessments (Table 1), including emergency room visits, unscheduled office visits, hospitalizations, and procedures for kidney stone management.

7. STATISTICS

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

7.1. Determination of Sample Size

The planned enrollment for this study is 120 patients.

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05. Table 7 shows the statistical power under various assumptions for a sample size of 40 per group.

Table 7: Sample Size Power Calculations

Assumed standard deviation (SD)	Assumed difference (lumasiran – placebo)	Power
25%	20%	94%
	30%	99%
30%	20%	84%
	30%	99%
45%	20%	50%
	30%	84%

Abbreviations: SD=standard deviation

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 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 at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Plasma Oxalate Analysis Set:** All patients who received at least 1 dose of study drug and have a baseline plasma oxalate level ≥1.5 times the lower limit of quantification/detection.

- **Safety Analysis Set:** All patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.
- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses.

7.2.2. Examination of Subgroups

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

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

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

7.2.5. Efficacy Analyses

The hypothesis testing for the primary endpoint will be tested comparing each lumasiran group to the placebo group in the FAS with a 2-sided significance level of 0.05.

The primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in urinary oxalate to Month 6 (average across Months 4 through 6). The model includes baseline 24-hour urinary oxalate and the stratification factor of number of historical kidney stone events (>1 versus ≤1 event in the 12 months prior to screening) as covariates, and fixed effect terms including treatment arm, visit and visit and treatment arm interaction. The estimate of treatment difference for the average percent change from baseline of 24-hour urinary oxalate excretion across Months 4 through 6 will be calculated via a linear contrast of the corresponding coefficients from the MMRM model.

Additionally, the percent change from baseline in 24-hour urinary oxalate excretion at Month 9 and Month 15 will be summarized and compared between lumasiran and placebo treatment groups.

Baseline, Month 9, and Month 15 urinary oxalate values and urinary calcium oxalate supersaturation values are planned to be collected in either duplicate or triplicate (baseline) and duplicate (Months 9 and 15), and the calculated median of valid collections during each time period (visit) will be used in the analysis.

Analysis of secondary endpoints and exploratory endpoints will be specified in the SAP. No multiplicity adjustment is planned.

7.2.6. Pharmacodynamic Analysis

The change in plasma and urinary PD parameters will be summarized over time for all patients in the FAS. For the change in plasma oxalate, a separate analysis population, the Plasma Oxalate Analysis Set will be used.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods.

Pharmacokinetic parameters to be calculated include but will not be limited to maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}). Other parameters may be calculated, if deemed necessary.

7.2.8. Safety Analyses

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

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

Descriptive statistics, summarizing the observed values and changes from baseline over time, will be provided for clinical laboratory parameters and vital signs. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Other Analyses

Other exploratory analyses will be described in the SAP.

7.2.11. Interim Analysis

No formal interim analysis is planned. The primary analysis will be conducted for the primary and secondary endpoints through Month 6 after the last patient has completed the Month 6 visit and the database is locked.

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 ICF (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 is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented. If circumstances warrant an updated informed consent during the study, and patients are required to re-consent, this may be collected remotely where local regulations allow.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. All patients will be given a copy of the signed and dated ICF.

8.1.2. Ethical Review

The study protocol, including the ICF, 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 or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent 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 6.5.5. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

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

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

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

8.1.3. Serious Breach of Protocol

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

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, 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 to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. 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 EOS is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

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

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

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

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

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

8.2.2. Study Monitoring

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

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

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for publications.

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

9. LIST OF REFERENCES

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10. APPENDICES

10.1. Formula for Estimated Glomerular Filtration Rate Calculation

Source: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

- $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black or African American]

  where:

  - S_{cr} is serum creatinine in mg/dL
  - $\kappa = 0.7$ (females) or 0.9 (males)
  - $\alpha = -0.329$ (female) or -0.411 (male)
  - $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
  - $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
  - Age (years)

Abbreviations: eGFR= Estimated glomerular filtration rate; SCr=serum creatinine

ALN-GO1-008 PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES DATED 07 JULY 2022 COMPARED TO PROTOCOL AMENDMENT 1 DATED 16 JUNE 2022

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose for this protocol amendment is to decrease participant burden and to simplify site execution by making computed tomography (CT) scans optional. The incidence rate of radiographic kidney stone events is an exploratory endpoint, and therefore this amendment is not considered to impact the scientific validity of the clinical study. Patients who elect to participate in optional CT scans will be requested to complete CT scans at both baseline and Month 15.

The location of clinical study centers was broadened globally to help with patient recruitment. The definition of permanent sterilization was also corrected based on guidance from the Clinical Trials Facilitation and Coordination Group (CTFG). Additionally, in the Schedule of Assessments, the Month 12/Day 337 Visit column was deleted as a correction to Protocol Amendment 1, because all assessments for the Month 12 visit were removed in Protocol Amendment 1.

A detailed summary of changes is provided in Section 2. The following changes are not detailed: administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. PROTOCOL AMENDMENT 2 DETAILED SUMMARY OF CHANGES

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

Purpose: Broaden the location of clinical study centers.

The primary change occurs in the Protocol Synopsis.

Revised text: The study will be conducted at approximately 55 clinical study centers ~~across~~ **worldwide including in** Europe and ~~United States~~ **North America**.

Purpose: Correction to the Schedule of Assessments based on Amendment 1

The primary change occurs in Table 1, Schedule of Assessments.

Deleted text (and column):

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]								Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period			
Study Visit			Baseline	M3	M4	M5	M6	EOT M9	~~M12~~	EOS/ ET M15	
Study Day (±Visit Window)	**Notes**	-60 to -1	Day 1	85 (±14)	113 (±7)	141 (±7)	169 (±14)	253 (±28)	~~337 (±7)~~	421 (±28)	3 and 6 months post last dose (±28)

Purpose: Corrected the definition of permanent sterilization.

The primary change occurs in Section 5.6.1, Contraception.

Revised text:

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

Purpose: Make CT scans optional.

The primary change occurs in Section 6.2.2.2, Radiographic.

Revised text:

> ~~A~~ **For patients who elect to participate in optional CT scans, a** non-contrast low-dose kidney-protocol CT scan will be performed ~~for all patients~~ on Day 1 (may be performed up to 3 days prior to Day 1), and at Month 15.
>
> For patients who **elect to participate in optional CT scans and** terminate the study early, a CT scan should be performed at the ET visit only if this visit occurs after Month 6 and at the discretion of the Investigator, and where permitted, following consultation with the Medical Monitor. **Optional** CT scans will be analyzed centrally.

Sections also reflecting this change:

- Table 1: Schedule of Assessments, including relevant footnotes.
- Section 3.1, Summary of Study Design
- Section 6, Study Assessments

Administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-GO1-008
DATED 16 JUNE 2022

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Short Title:	A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2021-001519-10
IND Number:	128941
Protocol Date:	Original protocol, 24 June 2021 Amendment 1, 16 June 2022
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

16-Jun-2022 | 11:09 PM EDT

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-008 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Short Title

A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Study Drug

Lumasiran (ALN-GO1)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 55 clinical study centers across Europe and the United States.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event

Objectives	Endpoints
• To evaluate additional pharmacodynamic (PD) parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize the pharmacokinetics (PK) of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of adverse events (AEs)

Study Design

This is a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered subcutaneously (SC) in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1).

Number of Planned Patients

The planned enrollment for this study is 120 patients.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years of age) with a documented diagnosis of recurrent kidney stone disease based on ≥2 stone events, with a minimum of 1 stone event within the 5 years prior to screening. A historical kidney stone event is defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on computed tomography (CT) imaging
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Study Drug, Dose, and Mode of Administration

Lumasiran (ALN-GO1) is a SC administered *N*-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA) targeting liver-expressed hydroxyacid oxidase (*HAO1*) messenger RNA (mRNA) for reduction of hepatic oxalate production.

Lumasiran will be administered by SC injection at a dose of 284 mg or 567 mg on Day 1, Month 3, and Month 9.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered at the same dosing interval as lumasiran.

Duration of Treatment and Study Participation

The duration of treatment with study drug is up to 15 months. The estimated total time on study for each patient is up to 17 months, including up to 2 months of screening.

Statistical Methods

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05.

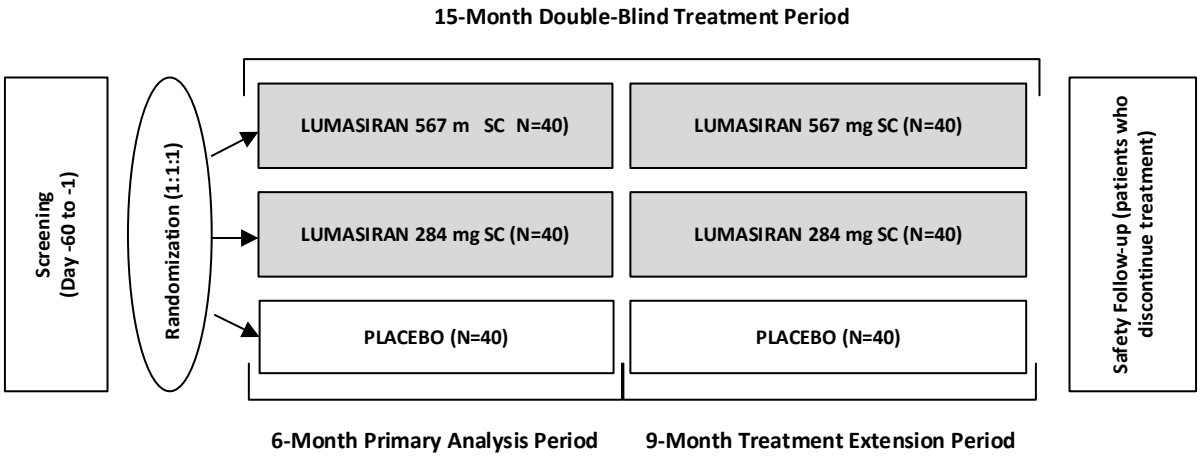
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients who received at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Plasma Oxalate Analysis Set:** All patients who received at least 1 dose of study drug and have a baseline plasma oxalate level ≥1.5 times the lower limit of quantification/detection.
- **Safety Analysis Set:** All randomized patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.
- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary efficacy endpoint will be analyzed in the FAS using a mixed-effect model for repeated measures (MMRM) approach. The primary comparison is percent change from baseline in urinary oxalate through Month 6.

Safety data will be summarized descriptively.

Figure 1: Study Design



Abbreviations: SC=subcutaneous(ly)

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]								Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period			
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**337 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Informed consent	Section 6.1	X									
Assign patient identification number	Section 3.4	X									
Demographics	Section 6.1	X									
Blood for DNA analysis	Unless tested previously, see Section 6.1.1	X									
Full physical examination	Section 6.5.3	X								X	
Follicle-stimulating hormone	To confirm postmenopausal status if applicable; Section 6.5.4.2	X									
Serum pregnancy test (for WOCBP)	See Section 6.5.4.2	X									

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]								Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period			
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**337 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
2 separate 24-hour urine collections	2 valid screening collections (see Section 6.2.1.1); an additional collection may be required (see Section 6.2.1.1) Collect within 14 days prior to dosing (M9) or visit (M15); repeat if invalid. See Table 4	X						X		X	
Inclusion/exclusion criteria	Section 4.1; Section 4.2	X	X[b]								
Medical history	Section 6.1	X	X								
Height	Section 6.5.2	X	X							X	
Vital signs	Section 6.5.1	X	X	X				X		X	X
Body weight	Section 6.5.2	X	X	X				X		X	X
Patient Diary	Diet compliance check and 24-hour urine collection; Section 5.6.3	X		X	X	X	X	X		X	

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]								Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period			
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**337 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Single 24-hour urine collection	Collect within 14 days prior to dosing (M3) or visit (M4, M5, M6); repeat if invalid. See Table 4			X	X	X	X				
Blood sample for PD analyses	Section 6.3	X	X	X			X	X		X	
Clinical laboratory assessments	Section 6.5.4	X	X	X			X	X		X	X
Antidrug antibody sample	Section 6.5.4.1		X	X			X	X		X	X
Urine pregnancy test (for WOCBP)[c]	May be performed more frequently where required per local requirements, or if pregnancy is suspected. See Section 6.5.4.2		X	X				X			
Symptom-directed physical examination	Section 6.5.3		X	X				X			X
Prior and concomitant medications	Section 5.4	Continuous									
Clinical kidney stone events	Section 6.2.2	Continuous									

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]								Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period					Treatment Extension Period			
Study Visit			**Baseline**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**337 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Review/record adverse events	Section 6.5.5	Continuous									
Healthcare utilization	Section 6.6	Continuous									
Randomization	Window: 1 business day prior to Day 1 for study drug preparation		X								
Blood samples for PK analyses	Table 2; Section 6.4		X								
Study drug administration	Section 5.2.2		X	X				X			
Low-dose kidney-protocol CT scan[d]	Section 6.2.2.2		X (-3 days window)							X	

Abbreviations: CT=computed tomography; D/C=discontinue; ET=early termination; EOS=end of study; EOT=end of treatment; M=month; PD=pharmacodynamic; PK=pharmacokinetic; WOCBP=women of child-bearing potential

Notes:

- When scheduled at the same time points, assessments of vital signs should be performed before physical examinations and blood sample collections, where feasible.
- Patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses (refer to Section 4.3.1).

- White columns indicate visits to the clinical study center; gray-shaded columns indicate study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion and with oversight of the Investigator, based on safety and tolerability), provided (for dosing visits) that the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a symptom-directed physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, kidney stone events, and adverse events.

Footnotes:

[a] **All assessments are required to be performed prior to dosing at dosing visits, except for the CT scan and PK 2-hour postdose sample collection.**

[b] Inclusion/exclusion criteria should be verified prior to randomization. Laboratory assessments conducted to confirm study eligibility will not be repeated unless the time between screening and randomization exceeds 4 weeks.

[c] Pregnancy test results must be known prior to dosing, if applicable.

[d] May be performed after dosing, if required.

Table 2: Pharmacokinetic Time Points

Study Day	Sampling Time (hh:mm)	Blood PK Sample
Day 1	Predose (any time before dosing)	X
	02:00 (±30 min)	X

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

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 7.2.7 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum plasma concentration
CPC	Clinical product complaint
CT	Computed tomography
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
ESKD	End stage kidney disease
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
GO	Glycolate oxidase
HAO1	Hydroxyacid oxidase 1
HED	Human equivalent dose
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamics
PH1/2/3	Primary hyperoxaluria type 1/2/3
PK	Pharmacokinetic
PT	Preferred term
RNAi	Ribonucleic acid interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) has developed 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*) messenger ribonucleic acid (mRNA), blocking production of glycolate oxidase (GO) and hence reducing hepatic oxalate production.

Lumasiran is approved for the treatment of primary hyperoxaluria type 1 (PH1) in both pediatric and adult patients in the United States (23 November 2020) and in the European Union (19 November 2020). Based on lumasiran's mechanism of action, and demonstrated reduction of hepatic oxalate production in patients with PH1, the Sponsor is investigating whether treatment with lumasiran is effective for patients with recurrent calcium oxalate kidney stone disease who have elevated urinary oxalate levels but have not been diagnosed with PH1 or one of the other primary hyperoxalurias.

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

1.1. Study Rationale

Study ALN-GO1-008 is a randomized, double-blind, placebo-controlled, multi-center Phase 2 study designed to evaluate the efficacy, safety, pharmacodynamics (PD), and pharmacokinetics (PK) of lumasiran, administered subcutaneously (SC), in adult patients with recurrent calcium oxalate kidney stone disease.

The primary objective of the study is to evaluate the effect of lumasiran on the percent change in urinary oxalate excretion in patients with recurrent calcium oxalate kidney stones. Secondary and exploratory objectives of the study include the evaluation of the effect of lumasiran on urinary calcium oxalate supersaturation, the occurrence of kidney stones, the PD effect of lumasiran on plasma oxalate, plasma glycolate and urinary glycolate, and the characterization of plasma PK.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Kidney stones are common, affecting approximately 1 in 11 people in the United States, and the prevalence of kidney stone disease has been increasing worldwide over time.[Scales 2012] Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals, with the remainder being predominantly calcium phosphate, uric acid, cystine, or struvite.[Worcester and Coe 2008; Worcester and Coe 2010] Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine (Figure 2). High levels of urinary oxalate may be derived from both endogenous synthesis and diet.

Kidney stones can develop in patients of all ages; however, the highest incidence rates occur in individuals aged 40 to 66 years.[Shin 2018] There is significant clinical burden associated with the development of kidney stones for patients with recurrent calcium oxalate kidney stone disease, including pain, infection/sepsis, diagnostic and therapeutic procedures, hospitalizations,

and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease (ESKD).

The typical clinical presentation of kidney stones includes sudden onset of lumbar flank pain and hematuria, and may include nausea and vomiting. Evaluation to assess etiology includes assessment of the patient's medical history, medication use, and dietary and lifestyle risk factors. Confirmation of diagnosis may involve renal ultrasound, abdominal x-ray, and/or computed tomography (CT).[Heilberg and Schor 2006] 24-hour urine collections analyzed for total volume, calcium, oxalate, uric acid, citrate, and other analytes may help to determine the underlying etiology.[Pearle 2014] Stone composition is generally determined in at least one instance.

There are limited effective treatment options for patients with recurrent calcium oxalate kidney stone disease. Preventive measures in American and European guidelines recommend adequate fluid intake to ensure a urine volume of at least 2 to 2.5 liters daily and provide dietary advice to limit the consumption of oxalate-rich foods, sodium chloride, and animal protein content, while maintaining a normal calcium intake. In some situations, thiazide diuretics, potassium citrate, and/or allopurinol may be considered.[Pearle 2014; Türk 2021]

Treatment of pain associated with kidney stone events may involve non-steroidal anti-inflammatory agents and/or opiate pain medications. Depending on the clinical context, medical expulsive therapy, extracorporeal shock-wave lithotripsy, ureteroscopy, stenting, and percutaneous nephrolithotomy are some of the treatment options that may be pursued.[Türk 2021]

Lumasiran is a ribonucleic acid interference (RNAi) therapeutic designed to reduce hepatic oxalate production. Oxalate produced by the liver is largely excreted in the urine, and lumasiran has been shown to reduce urinary oxalate in patients with PH1. High levels of urinary oxalate increase the risk of stone formation; therefore, lumasiran may have efficacy in patients with recurrent calcium oxalate kidney stone disease who do not have PH1 but who produce high amounts of oxalate endogenously.

1.3. Benefit-Risk Assessment

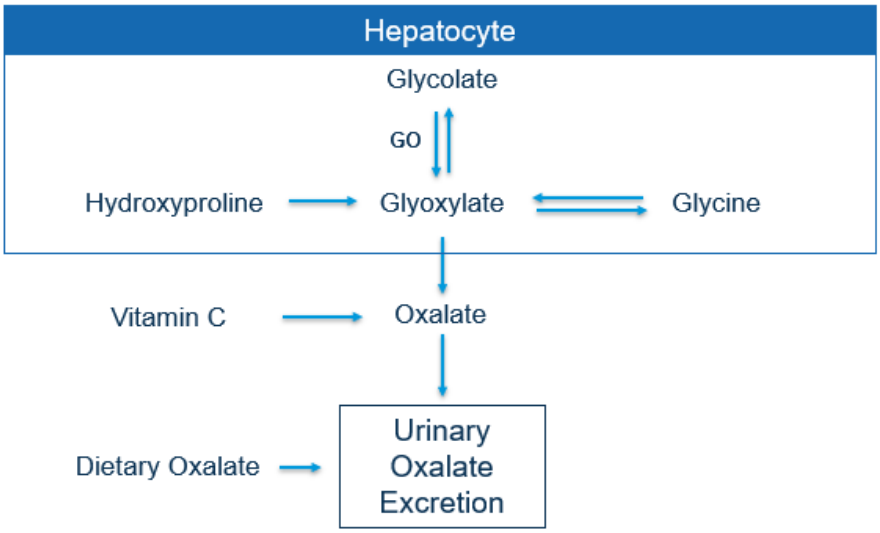
Calcium oxalate stone formation occurs when a supersaturating level of calcium oxalate is present in the urine, with increasing risk of stone formation as urine oxalate levels increase.[Curhan and Taylor 2008] More than half of oxalate is endogenous in origin and presumed to come largely from the liver.[Mitchell 2018] Studies have shown that reduced calcium oxalate supersaturation and urinary oxalate levels are associated with reduced stone formation.[Borghi 2002; Ferraro 2018; Prochaska 2018]

For patients with recurrent calcium oxalate stone formation, multiple stone removal procedures may be required. These procedures are invasive and place the patient at risk of complications including bleeding and infection. Patients experiencing obstructive kidney stones can also experience acute kidney injury with permanent loss of renal function. As a result, patients with recurrent kidney stone formation have a higher risk of progression to CKD and ESKD.[Dhondup 2018; Rule 2009]

Lumasiran, approved in the United States and European Union for the treatment of PH1, is designed to reduce hepatic production of oxalate. Based on the available data from clinical and

nonclinical studies, lumasiran, administered SC, demonstrated a potent, dose-dependent inhibition of GO resulting in decreased urinary and plasma oxalate and increased plasma and urinary glycolate. Lumasiran may be effective in lowering urinary oxalate levels in patients with recurrent calcium oxalate kidney stone disease (Figure 2). No adverse effects of elevated glycolate have been reported. Unlike oxalate, glycolate is highly soluble and readily excreted in the urine.

Figure 2: Summary of Endogenous Oxalate Synthesis



Abbreviations: GO=glycolate oxidase

Lumasiran has been well tolerated with an acceptable safety profile in studies with healthy volunteers and patients with PH1. Most adverse events (AEs) have been mild or moderate in severity. Transient, mild injection site reactions (ISRs) have been observed. No clinically significant laboratory changes related to lumasiran 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 hepatic effects. The study has specific 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 (LFTs). As the risk of embryofetal toxicity in humans is currently unknown, females who are of child-bearing potential during the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use contraception as specified in the protocol (see Section 5.6.1).

Based on the available efficacy and safety data from clinical and nonclinical studies, the benefit-risk assessment supports the evaluation of lumasiran in a Phase 2 study in patients with recurrent calcium oxalate kidney stone disease.

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

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event
• To evaluate additional PD parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize PK of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6

Objectives	Endpoints
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of AEs

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered SC in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

The study will consist of up to 2 months of screening and 15 months of double-blind treatment (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period). Patients will be screened from Day -60 to Day -1 to determine eligibility. During screening, patients will provide at least two 24-hour urine collections to establish baseline urinary oxalate levels. Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1), as discussed in Section 3.4.

During the 6-month Primary Analysis Period, patients will be dosed on Day 1 (baseline) and at Month 3. During the Treatment Extension Period, one additional dose will be administered at Month 9; an end of study (EOS) visit will take place at Month 15. Study drug will be administered SC as specified in Section 5.2.2. Patients will be assessed for efficacy, safety, PD, and PK according to the Schedule of Assessments (Table 1 and Table 2). Efficacy assessments will include evaluation of urinary oxalate excretion, urinary calcium oxalate supersaturation, and kidney stone events (including clinical events and low-dose kidney-protocol CT). Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, physical examinations, and concomitant medications.

Patients who discontinue study drug early will be asked to return for follow-up visits as described in Section 4.3.1.

3.2. Scientific Rationale for Study Design

The primary endpoint for this Phase 2 study is the percent change in 24-hour urinary oxalate excretion. To confirm the optimal dosing regimen, and to facilitate the collection of kidney

stone event data (an exploratory endpoint), the study will continue through Month 15. A placebo comparator is included because there is no approved standard of care therapy to decrease urinary oxalate.

A blood DNA sample will be collected as part of standard screening assessments (if testing has not already been performed) to ensure the exclusion of patients with primary hyperoxaluria type 1 (PH1), type 2 (PH2), and type 3 (PH3). Lumasiran is approved in some countries for the treatment of PH1, and patients with PH2 and PH3 are not expected to respond to lumasiran.

Because the primary endpoint will rely on measurements of urinary oxalate, and because some urinary oxalate is diet-derived, diet is an important variable in this study. In a 5-year study of recurrent stone formers published by Borghi et al, patients randomized to a normal calcium, low protein/salt diet had lower urinary oxalate levels and a lower cumulative incidence of recurrent kidney stones when compared to a low calcium diet. During the current study, and as of the time of informed consent, patients will be asked to adhere to a diet appropriate for stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate.

The secondary endpoint to assess meaningful reduction in 24-hour urinary oxalate from baseline to Month 6 (Months 4 through 6) defines a clinically meaningful reduction as ≥20% in the non-PH1 stone former population, supported by available literature based on stone former populations.[Borghi 2002]

In this study, lumasiran will be evaluated in patients with recurrent calcium oxalate kidney stone disease. Due to the limited and burdensome disease management options, there is an unmet need for new therapies.

3.3. Justification for Dose

Two dose levels of lumasiran 284 and 567 mg given on Day 1, Month 3, and Month 9 were selected to evaluate urinary oxalate dose response. The higher dose level of 567 mg is expected to suppress GO enzyme by ≥95%, comparable to the regimen evaluated in ALN-GO1-003 (ILLUMINATE-A) in patients with PH1. The lower dose of 284 mg is expected to suppress GO enzyme by 90%. In addition, the fixed doses will simplify dose administration in this adult study population. Both regimens are predicted to achieve near-steady state ribonucleic acid-induced silencing complex (RISC) concentrations and urinary oxalate suppression at Month 6. Month 9 dosing is intended to sustain PD effect through Month 15 and will provide data to differentiate the effect of every 3 months and every 6 months dosing on urinary oxalate reduction.

Single 0.3 to 6.0 mg/kg doses of lumasiran in healthy subjects and multiple 3.0 mg/kg doses of lumasiran administered monthly or once every 3 months in patients with PH1 have been well tolerated. Plasma and liver exposure for the lumasiran 284 and 567 mg doses are expected to be in the range of 3.0 to 6.0 mg/kg lumasiran doses evaluated in healthy subjects in ALN-GO1-001 (Part A) and patients with PH1 in ALN-GO1-001 (Part B), ALN-GO1-002, and ILLUMINATE-A. Based on rat and monkey NOAEL doses of lumasiran 200 mg/kg and 300 mg/kg, a sufficient safety margin exists for the use of lumasiran 284 and 567 mg doses (refer to the ALN-GO1 Investigator Brochure).

Based on a 70 kg patient, the planned doses of 284 mg and 567 mg equate to approximately 4.0 mg/kg or 8.0 mg/kg, respectively. The human equivalent dose (HED) margin values for the

approximate 4 mg/kg clinical dose were 8.1-fold for the chronic rat study and 24.2-fold for the chronic monkey study; the HED margin values for the approximate 8.0 mg/kg clinical dose were 4.0-fold for the chronic rat study and 12.1-fold for the chronic monkey study (refer to the ALN-GO1 Investigator Brochure).

3.4. Method of Assigning Patients to Treatment Groups

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. After the patient signs the informed consent form (ICF) and before proceeding with screening procedures, the Investigator or his/her designee will contact the Interactive Response Technology (IRT) to obtain a patient identification number.

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

Patients will be randomized 1:1:1 to receive lumasiran 284 mg, lumasiran 567 mg, or placebo, administered at the same volume (see Section 5.2.2), for the duration of the study. Stratification will be performed at randomization according to baseline urinary oxalate level (≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1).

For stratification, the number of historical kidney stone events occurring in the 12 months prior to screening are considered, and defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 12 months prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

3.5. Blinding

Site personnel and patients will be blinded to study drug treatment; site personnel preparing study drug may be unblinded to study drug treatment only where required by documented institutional procedure. The Sponsor will have access to unblinded study data during the conduct of the study. Lumasiran and placebo will be packaged identically and will be administered at the same volume under the supervision of the Investigator at the study center or by a healthcare professional at the patient's home (see Section 5.2.2). Since lumasiran may be visually

distinguishable from placebo, the syringe will be masked prior to administration by a healthcare professional. See the Pharmacy Manual for additional details.

All site personnel will be blinded to laboratory results of oxalate, calcium oxalate supersaturation, and glycolate from after the time of the first dose until unblinding. Results will not be reported to the Investigator from the first dose until the last patient completes assessments at the Month 15 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 measurements for oxalate, calcium oxalate supersaturation, or glycolate from the first dose until the sites and patients are unblinded, or until the patient ends the study, whichever is earlier. If oxalate, calcium oxalate supersaturation, or glycolate are 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.

Any unplanned unblinding occurring during the study period will be documented and reported in the clinical study report.

3.5.1. 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. If contact prior to unblinding is not possible, personnel must contact the Medical Monitor 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 trial master file.

Refer to the IRT instructions for details on unblinding.

3.6. Safety Review

A safety review committee will not be utilized for this study; however, the Sponsor will monitor safety on an ongoing basis and in accordance with the Sponsor's internal processes.

3.7. Definition of End of Study for an Individual Patient

A patient is considered to have reached the EOS if the patient:

- has completed the EOS (Month 15) visit, or
- has completed safety monitoring following the final dose of study drug as described in Section 4.3.1

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

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

Age

1. Age 18 years or older (or age of legal consent, whichever is older).

Patient and Disease Characteristics

2. Recurrent kidney stone disease, defined as ≥2 stone events, with a minimum of 1 stone event within the 5 years prior to screening. For inclusion, a historical kidney stone event is defined as:
   - the visible passage of a kidney stone
   - a procedural intervention for removal of an asymptomatic or symptomatic stone
     - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
     - if more than 1 procedure was required to remove a single stone, this counts as 1 event
   - a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
     - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.
3. The 2 most recently analyzed kidney stones prior to randomization contained 50% or more of calcium oxalate; if only one stone analysis is available, then it must have contained 50% or more of calcium oxalate.
4. 24-hour urinary oxalate levels from 2 valid 24-hour urine collections obtained during screening are >ULN (ULN = 40 mg/24 hours).
5. Willing to adhere to dietary recommendations appropriate for stone formers including limiting vitamin C supplementation to <200 mg daily.
6. If taking medications and/or hydrating for kidney stone prophylaxis, or taking medications that alter urinary oxalate excretion and/or kidney stone formation, must have been on a stable regimen for at least 60 days before randomization, and willing to remain on this stable regimen for the duration of the study.
7. Body mass index (the weight in kilograms divided by the square of the height in meters) at screening of 20 to <40 kg/m^2.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

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

Laboratory Assessments

1. Has any of the following laboratory parameter assessments at screening:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN
    b. Total bilirubin >1.5 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
2. Has an eGFR of <30 mL/min/1.73m^2 at screening (calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine formula; see Section 10.1).

Prior/Concomitant Therapy

3. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.

Medical Conditions

4. Patients with a known history of secondary causes of elevated urinary oxalate and/or recurrent kidney stones including:
    a. Primary hyperoxaluria
    b. Severe eating disorders (anorexia or bulimia)
    c. Chronic inflammatory bowel disease
    d. Intestinal surgery with malabsorption or chronic diarrhea
    e. Sarcoidosis
    f. Primary hyperparathyroidism
    g. Complete distal renal tubular acidosis
5. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
6. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
7. History of intolerance to SC injection(s).

Contraception, Pregnancy, and Breastfeeding

8. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.6.1.
9. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol Use

10. 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]).
11. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.

4.3. Removal from Study Drug or Assessment

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

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

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

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

- Significant protocol deviation
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.5.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

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

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of

the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including serious adverse events (SAEs), the event should be followed as described in Section 6.5.5. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month Primary Analysis Period (defined as a discontinuation that occurs after the first dose of study drug administration on Day 1 during the 6-month Primary Analysis Period) will be encouraged to remain on the study and complete all assessments (including 24-hour urine collections) through Month 6, with early termination (ET) assessments at Month 9, and safety follow-up per the safety follow-up schedule (Table 1). Patients who do not remain on the study through Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete safety follow-up per the safety follow-up schedule (Table 1).

Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete a safety follow-up visit per the safety follow-up schedule (see Table 1).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the ET assessments (see Table 1).

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

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

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

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

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

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments through the Primary Analysis Period (Month 6).

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

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

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.5.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient 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 continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (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.

- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

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

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug (lumasiran and placebo) 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 study drug 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

Patients will be administered SC injections of lumasiran (284 mg or 567 mg) and/or placebo at the same volume, as described below, on Day 1, Month 3, and Month 9.

Lumasiran 567 mg	**Lumasiran 284 mg**	**Placebo**
1.5 mL lumasiran 1.5 mL lumasiran	1.5 mL lumasiran 1.5 mL placebo	1.5 mL placebo 1.5 mL placebo

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, syringes are to be masked prior to the removal of study drug from vials. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be permitted at a location other than the study center (for example, the patient's home) by a healthcare professional with the oversight of the Investigator, provided the patient has tolerated at least 1 dose of study drug administered in the clinic. However, continued study

drug administration at the study center should be considered for patients who have ongoing study drug-related AEs 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 visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.5.8.

5.2.3. Dose Modifications

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. Results of previous LFT assessment 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 3.
3. For any ALT or AST elevation >3× ULN:
    a. If local laboratory results are obtained, confirm with a 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 5 and Table 6.
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 3.

Table 3: 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least every 2 weeks: LFT per Table 5 • 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 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. • Evaluate the initial elevation in LFT per the following assessments until satisfactory resolution: – Table 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; 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. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically non-medical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For CPCs, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. Clinical product complaints that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.5. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Concomitant Medications and Procedures

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

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

Standard vitamins and topical medications are permitted (vitamin C supplementation must be <200 mg daily per inclusion criteria). However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

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.

5.5. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.6. Other Requirements

5.6.1. Contraception

Females of child-bearing potential must be willing to use an acceptable method of contraception from 14 days before first dose, throughout study participation, and for 6 months after last dose administration or until study completion.

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 (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and for up to 6 months after the last dose of study drug.

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

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by a 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, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.4.2).

5.6.2. 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.

5.6.3. Dietary Restrictions

For the duration of the study patients should adhere to a diet appropriate for calcium oxalate stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate. Details are provided in the Dietary Reference Sheet.

Dietary adherence will be collected in a patient diary at the time points listed in the Schedule of Assessments (Table 1). Refer to the Study Manual for more information.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1. All assessments are required to be performed prior to dosing at dosing visits, except for CT imaging and PK 2-hour postdose sample collection. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, and as noted in Table 1, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include pregnancy testing (urine or serum), clinical laboratory assessments, urine collections, DNA testing, symptom-directed physical examination / body system assessment, vital signs, body weight, height, blood collection for PD and ADA analyses (at the discretion and with oversight of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed by the patient before the screening procedures are initiated. All patients will be given a signed and dated version of their ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. To confirm study entrance criteria, 24-hour urine will be collected per Table 4.

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and prior to dosing will be updated.

6.1.1. DNA Sample

A blood sample for DNA analysis will be collected from all patients as part of the screening assessments. The samples will be analyzed for PH1, PH2, and PH3 (unless tested previously) to confirm eligibility (see Section 4.2). Refer to the Laboratory Manual for more information.

6.1.2. Retesting

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

6.1.3. Rescreening

Rescreening of patients is permitted with approval of the Medical Monitor. 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 be allowed to return for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment with study drug. The site should update the patient's status in the IRT to reflect this as soon as possible.

6.2. Efficacy Assessments

Efficacy assessments are to be performed as specified in the Schedule of Assessments (Table 1).

6.2.1. 24-Hour Urine Collections

Urinary oxalate excretion and calcium oxalate supersaturation (calculated from multiple parameters) will be determined from 24-hour urine sample collections to be completed at the time points specified in the Schedule of Assessment (Table 1). The start and stop dates/times of collection, the volume of urine in the collection, whether there were any missed voids, and whether the patient complied with dietary recommendations will be recorded. An aliquot of the 24-hour urine collection will also be used to determine urinary creatinine content and to determine if the 24-hour urine collections need to be repeated (see Section 6.2.1.1).

The 24-hour urine collection procedure by study visit is provided in Table 4.

Table 4: 24-hour Urine Collection Procedure by Study Visit

Study Visit and Urine Collection Window	**Number of Collections to Schedule**	**Validity Requirement Prior to Dosing/Visit** (see Section 6.2.1.1)	**Notes**
Screening (within 60-day period)	2	2 valid collections prior to dosing unless variability criterion is not met (Section 6.2.1.2), in which case an additional collection is required[a].	Supervised collections[b] are encouraged unless patient is already familiar with the collection procedure. If any collections are invalid, the remaining collections for screening must be supervised.
Months 3, 4, 5, and 6 (within 14 days prior to dosing/visit)	1	No	If an invalid collection is obtained for the timepoint, a single repeat collection must be supervised. Repeat collection, if necessary, is to be completed within ±14 days of dosing/visit.
Months 9 and 15 (within 14 days prior to dosing/visit)	2	1 valid collection prior to dosing/visit	If a patient has had ≥2 prior invalid collections, both collections at these visits must be supervised[b]. At least 1 valid collection must be obtained prior to dosing/visit. If any collections for the timepoint are invalid, the remaining collection(s) for the timepoint must be supervised.

[a] The additional collection is not required to be valid in order to proceed with dosing, but will be tested to confirm validity for the calculation of baseline 24-hour urinary oxalate.

[b] A supervised collection is defined, at a minimum, as contact from study staff to the patient the day prior to the collection start and the day the collection will finish to ensure compliance; this may be conducted remotely. Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine collection is not a supervised collection, or if a collection is supervised remotely, patients may either bring it to the clinic or have it couriered to the clinic.

6.2.1.1. Validity Criteria for 24-hour Urine Collections

Throughout the study, a urine collection will be considered valid if each of the following criteria are met:

- The collection is between 22 to 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.
- Patient complied with dietary recommendations appropriate for oxalate stone formers (detailed in the Dietary Reference Sheet) for the 4 days prior to the start of the urine collection and during the collection.

24-hour urine collections that are known to be invalid should still be submitted for analysis.

6.2.1.2. Variability Criterion for 24-hour Urine Collections at Screening

If the 2 valid 24-hour urine collections from screening meet eligibility requirements (both 24-hour urinary oxalate levels >ULN), the variability between the oxalate levels (in mg/day) should be assessed as follows:

$$Variability = \left|\frac{(Oxalate\ value\ \#1 - Oxalate\ value\ \#2)}{(Average\ of\ oxalate\ values\ \#1\ \&\ \#2)}\right| \times 100\%$$

If the variability is >20%, then an additional 24-hour urine collection should be obtained. The result of the additional sample will not impact the patient's eligibility for the study.

6.2.2. Kidney Stone Events

Since kidney stone events are recorded as an efficacy assessment, these events will not be captured as AEs or SAEs. However, if a patient experiences other AEs or SAEs during a kidney stone event, they should be reported as an AE (see Section 6.5.5.2).

Kidney stone events will be graded by the Investigator as mild, moderate, or severe as defined in Section 6.5.5.1. If there are changes in grade during an event, only the highest grade should be reported.

6.2.2.1. Clinical

All relevant clinical information pertaining to a kidney stone events should be obtained, including laboratory values, medical records, discharge summaries, and medical test results (including stone composition, if available, and radiology reports). A clinical kidney stone event is defined as one of the following:

- Visible passage of a kidney stone
- A procedural intervention for removal of an asymptomatic or symptomatic stone (information on the location, number, and size of stones removed will be collected)

- Or, in the case of potential stone passages without visible stones, it will be up to the Investigator to evaluate patients' symptoms and determine whether a stone passage occurred or the symptoms were due to a different cause.

6.2.2.2. Radiographic

A non-contrast low-dose kidney-protocol CT scan will be performed for all patients on Day 1 (may be performed up to 3 days prior to Day 1), and at Month 15.

For patients who terminate the study early, a CT scan should be performed at the ET visit only if this visit occurs after Month 6 and at the discretion of the Investigator, and where permitted, following consultation with the Medical Monitor. CT scans will be analyzed centrally.

6.2.3. Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR (mL/min/1.73m^2) will be obtained at the time points specified in the Schedule of Assessment (Table 1).

eGFR will be calculated based on the CKD-EPI formula (see Section 10.1).[Levey 2009; Schwartz 2009]

6.3. Pharmacodynamic Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma oxalate and plasma glycolate, and 24-hour urinary glycolate) at the time points specified in the Schedule of Assessments (Table 1). On dosing days, all blood and urine samples will be collected prior to study drug administration.

All PD assessments will be analyzed centrally. Postdose PD results will not be distributed to the sites until after the last patient completes assessments at the Month 15 visit. Site personnel should refrain from obtaining or viewing local oxalate, calcium oxalate supersaturation, or glycolate assessments, except as medically indicated, due to risk of unblinding (Section 3.5). Details regarding the processing and aliquoting of PD samples for shipping and storage are provided in the Laboratory Manual.

Where local regulations allow and infrastructure is in place, a healthcare professional may collect urine or blood samples offsite.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of lumasiran PK parameters at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

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

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight

and height, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded as either medical history or AEs, as appropriate.

Safety assessments are to be performed as specified in the Schedule of Assessments (Table 1). On dosing days and as applicable, assessments of vital signs, weight/height, physical examination, and clinical laboratory assessments are to be completed before study drug administration.

Adverse event assessments are detailed under Section 6.5.5.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. 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 predose in the seated or supine position, after the patient has rested comfortably for approximately 5 minutes. Blood pressure should be taken using the same arm when feasible. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

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

Vital signs results will be recorded in the eCRF.

6.5.2. Height and Weight

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); 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. If a visit is conducted offsite (eg, home), a body system assessment may be performed in lieu of a physical examination.

Symptom-directed physical examinations will be guided by evaluation of ongoing symptoms, changes in symptoms, or the onset of new symptoms, since the last visit. If there are no ongoing symptoms, changes in symptoms, or new symptoms, then a symptom-directed physical examination is not required.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history eCRF (if observed during screening) or the AE eCRF (if observed at any post-screening visit).

6.5.4. 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. Laboratory assessments conducted to confirm study eligibility (Section 4) will not be repeated unless the time between screening and randomization exceeds 4 weeks. 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, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and included in the clinical database. Clinical laboratory assessments are listed in Table 5 and will be assessed as specified in the Schedule of Assessments (see Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of visit assessments, all laboratory assessments specified in Table 5 which are performed at a local laboratory should also be sent in parallel to the central laboratory. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results on samples drawn on the same day.

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 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR[a]	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Coagulation	
International Normalized Ratio (screening only)	
Immunogenicity (see Section 6.5.4.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.4.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone
[a] Refer to Section 10.1 and the laboratory manual for further instructions on calculating eGFR.

6.5.4.1. Immunogenicity

Blood samples will be collected to evaluate ADA. Blood samples for ADA testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1).

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

6.5.4.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed thereafter per the Schedule 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 that is 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 6.5.5.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm postmenopausal status in all women suspected to be postmenopausal. Postmenopausal women and women who are permanently sterilized will not undergo pregnancy testing.

6.5.4.3. 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 (see Table 3). Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments per Table 3, and other assessments or evaluations per Investigator discretion, as appropriate.

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

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

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

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

Note:

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

6.5.5. Adverse Events

6.5.5.1. Definitions

Adverse Event

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

Serious Adverse Event

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

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

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3× ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or ISRs 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 6.5.5.2 and Section 6.5.5.3, 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 AE.

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

Adverse event 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.

6.5.5.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient 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, 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 EOS. Non-serious AEs will be followed until the EOS. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the EOS. Serious AEs 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 the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to eCRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

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

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

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), 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 eCRF 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).

6.5.5.4. 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 6.5.5.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious

- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious AEs 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.

6.5.5.5. 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.

6.5.5.6. 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.

6.5.5.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 6 months following the last dose of study drug, 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 6 months 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 6.5.5.4.

The reporting of any pregnancy outcome for a female partner of a male patient participating in this study that results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly should be reported to the Investigator, who will then report this to the Sponsor or designee. The pregnancy outcome is to be recorded on the pregnancy reporting form.

6.5.5.8. Reporting of Overdose and Other Special Situations

An overdose is defined as any dose of study drug administered to the participant that is ≥2-fold the assigned dose during a single administration.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs. Overdose per se will not be categorized as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported as an SAE regardless of sequelae.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Healthcare Utilization

To complement medical records, information regarding health resource use related to kidney stone events will be collected as specified in the Schedule of Assessments (Table 1), including emergency room visits, unscheduled office visits, hospitalizations, and procedures for kidney stone management.

7. STATISTICS

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

7.1. Determination of Sample Size

The planned enrollment for this study is 120 patients.

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05. Table 7 shows the statistical power under various assumptions for a sample size of 40 per group.

Table 7: Sample Size Power Calculations

Assumed standard deviation (SD)	Assumed difference (lumasiran – placebo)	Power
25%	20%	94%
	30%	99%
30%	20%	84%
	30%	99%
45%	20%	50%
	30%	84%

Abbreviations: SD=standard deviation

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 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 at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Plasma Oxalate Analysis Set:** All patients who received at least 1 dose of study drug and have a baseline plasma oxalate level ≥1.5 times the lower limit of quantification/detection.

- **Safety Analysis Set:** All patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.
- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses.

7.2.2. Examination of Subgroups

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

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

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

7.2.5. Efficacy Analyses

The hypothesis testing for the primary endpoint will be tested comparing each lumasiran group to the placebo group in the FAS with a 2-sided significance level of 0.05.

The primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in urinary oxalate to Month 6 (average across Months 4 through 6). The model includes baseline 24-hour urinary oxalate and the stratification factor of number of historical kidney stone events (>1 versus ≤1 event in the 12 months prior to screening) as covariates, and fixed effect terms including treatment arm, visit and visit and treatment arm interaction. The estimate of treatment difference for the average percent change from baseline of 24-hour urinary oxalate excretion across Months 4 through 6 will be calculated via a linear contrast of the corresponding coefficients from the MMRM model.

Additionally, the percent change from baseline in 24-hour urinary oxalate excretion at Month 9 and Month 15 will be summarized and compared between lumasiran and placebo treatment groups.

Baseline, Month 9, and Month 15 urinary oxalate values and urinary calcium oxalate supersaturation values are planned to be collected in either duplicate or triplicate (baseline) and duplicate (Months 9 and 15), and the calculated median of valid collections during each time period (visit) will be used in the analysis.

Analysis of secondary endpoints and exploratory endpoints will be specified in the SAP. No multiplicity adjustment is planned.

7.2.6. Pharmacodynamic Analysis

The change in plasma and urinary PD parameters will be summarized over time for all patients in the FAS. For the change in plasma oxalate, a separate analysis population, the Plasma Oxalate Analysis Set will be used.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods.

Pharmacokinetic parameters to be calculated include but will not be limited to maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}). Other parameters may be calculated, if deemed necessary.

7.2.8. Safety Analyses

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

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

Descriptive statistics, summarizing the observed values and changes from baseline over time, will be provided for clinical laboratory parameters and vital signs. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Other Analyses

Other exploratory analyses will be described in the SAP.

7.2.11. Interim Analysis

No formal interim analysis is planned. The primary analysis will be conducted for the primary and secondary endpoints through Month 6 after the last patient has completed the Month 6 visit and the database is locked.

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 ICF (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 is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented. If circumstances warrant an updated informed consent during the study, and patients are required to re-consent, this may be collected remotely where local regulations allow.

The patient's signed and dated informed consent must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. All patients will be given a copy of the signed and dated ICF.

8.1.2. Ethical Review

The study protocol, including the ICF, 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 or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent 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 6.5.5. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

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

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

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

8.1.3. Serious Breach of Protocol

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

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, 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 to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. 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 EOS is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

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

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

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

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

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

8.2.2. Study Monitoring

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

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

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for 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. Formula for Estimated Glomerular Filtration Rate Calculation

Source: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

- $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if Black or African American]

  where:

  - S_{cr} is serum creatinine in mg/dL
  - $\kappa = 0.7$ (females) or 0.9 (males)
  - $\alpha = -0.329$ (female) or -0.411 (male)
  - $\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
  - $\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
  - Age (years)

Abbreviations: eGFR= Estimated glomerular filtration rate; SCr=serum creatinine

ALN-GO1-008 PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES DATED 16 JUNE 2022
COMPARED TO ORIGINAL PROTOCOL DATED 24 JUNE 2021

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose for this protocol amendment is to decrease participant burden and to simplify site execution.

Inclusion Criterion

- Expanded Inclusion Criterion 2 to allow ≥2 stone events with a minimum of 1 stone required in the 5 years prior to screening. Rationale: To widen eligibility criteria from ≥2 stones in the previous 5 years to help with patient recruitment.

Outcome Assessments

- Removed exploratory endpoint of change from baseline in spot urinary oxalate:creatinine ratios and corresponding spot urine assessments from schedule of assessments. Rationale: To reduce participant burden and to simplify site execution.
- Removed all exploratory blood and urine samples including exploratory DNA assessments. Rationale: To simplify site execution.
- Removed electronic diary modality option from the patient diary for urine collection and dietary restriction details. Rationale: To reduce participant burden including technology-related considerations and to simplify site execution.
- Removed all patient-reported outcomes, including Brief Pain Inventory Short Form and Wisconsin Stone Quality of Life. Rationale: To reduce participant burden including technology-related considerations and to simplify site execution.

Schedule of Assessments

- Removed validity requirement before dosing if an additional 24-hour urine sample is required during screening (also in Section 6.2.1, Table 4 and in Section 6.2.1.2). Rationale: To reduce participant burden at the Day 1 visit. There is already flexibility in urine validity requirements prior to dosing/visit activities at the Month (M)3, M4, M5, M6, M9, and M15 visits in the Schedule of Assessments (Protocol Table 4). It is expected that most participants will not be required to collect an additional 24-hour urine sample, and the risk of a participant submitting an invalid collection after 2 confirmed valid collections in the screening period is deemed to be low. A sensitivity analysis is planned to account for any participants whose additional screening urine collection is found to be invalid.
- Removed urinalysis from clinical laboratory assessments (also in Section 6.5.4). Rationale: To reduce participant burden and to simplify site execution.

Pharmacokinetic Time Points

- Added predose pharmacokinetic (PK) time point to protocol Table 2.
  Rationale: Clarification that a predose sample is required.
- Removed PK time point of 4 hours post-dose from protocol Table 2. Rationale: To reduce participant burden.

Several additional changes are being implemented as outlined below.

Additional Changes:

- The number of sites was changed from approximately 25 to approximately 55 to help with patient recruitment.
- The Schedule of Assessments Visit Day for Month 12 was corrected from 309 to 337.
- In Section 3.1 and Section 3.4, language describing stratification was clarified to align with the study Statistical Analysis Plan (SAP).
- In Section 3.5, laboratory language was clarified to remove "central," and blinding language was clarified to allow unblinded site personnel to prepare study drug in accordance with documented institutional procedures.
- In Section 4.1:
  - Inclusion Criterion 4 was changed to clarify the upper limit of normal (ULN) for 24-hour urinary oxalate.
  - Inclusion Criterion 7 was changed to clarify that body mass index (BMI) is at screening.
- In Section 6.1, informed consent form (ICF) language was modified because electronic format is not available without the electronic diary modality.
- In Section 6.2.1, language was clarified to allow patients to have 24-hour urine collection samples couriered to the clinic.
- In Section 6.2.1.2, language was clarified regarding the collection of additional 24-hour urine samples.
- In Section 7 and Section 7.2.11, blinding language was clarified.
- In Section 7.2.1:
  - The Plasma Oxalate Analysis Set was added to align with the study SAP.
  - Language for the Safety Analysis Set was clarified.
- In Section 7.2.5, language for the mixed-effect model for repeated measures (MMRM) was clarified to align with the study SAP.
- In Section 7.2.6, the Plasma Oxalate Analysis Set was added to align with the study SAP.

- In Appendix 10.1, the formula provided was corrected to reflect the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimated glomerular filtration rate (eGFR) calculation.

A detailed summary of changes is provided in Section 2. The following changes are not detailed: administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. 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: Expand the number of sites from approximately 25 to approximately 55.

The change occurs in the Protocol Synopsis.

Revised text: The study will be conducted at approximately ~~25~~**55** clinical study centers across Europe and the United States.

Purpose: Remove exploratory endpoint of change from baseline in spot urinary oxalate:creatinine ratios and corresponding spot urine assessments.

The primary change occurs in Section 2, Objectives and Endpoints.

Removed text:

Objectives

- ~~To evaluate the effect of lumasiran on spot urinary oxalate:creatinine ratios~~.

Endpoints

- ~~Change from baseline in spot urinary oxalate:creatinine ratios~~

Sections also reflecting this change:

- Table 1: Schedule of Assessments; spot urine assessments were removed from all study visits.
- Section 6.2.3, ~~Spot Urinary Oxalate:Creatinine Ratios~~ (removed)

Purpose: Removed all patient-reported outcomes, including Brief Pain Inventory Short Form and Wisconsin Stone Quality of Life.

The primary change occurs in Section 2, Objectives and Endpoints.

Removed text:

Objectives

- ~~To assess the impact of kidney stone events on patient-reported pain and quality of life (QoL)~~.

Endpoints

- ~~Patient-reported severity and symptomatic and functional impact of kidney stone events~~

Sections also reflecting this change:

- Table 1: Schedule of Assessments; patient reported outcomes were removed from all study visits.
- Section 6.7, ~~Quality of Life Outcomes~~ (removed)

Purpose: Clarify language describing stratification to align with the study SAP.

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

Revised text: Stratification will be performed at randomization according to ~~mean~~ baseline urinary oxalate level **(≤1.25 × ULN vs >1.25 × ULN) from the mean of the first 2 valid 24-hour urine collections** and the number of **historical** kidney stone events in the 12 months prior to screening **(≤1 vs >1),** as discussed in Section 3.4.

Sections also reflecting this change:

- Protocol Synopsis
- Section 3.4, Method of Assigning Patients to Treatment Groups

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Purpose: Clarify language describing stratification to align with changes to Inclusion Criterion 2.

The change occurs in Section 3.4, Method of Assigning Patients to Treatment Groups.

Revised text:

For stratification, ~~a~~**the number of** historical kidney stone ~~event is~~**events occurring in the 12 months prior to screening are considered, and** defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging

~~– it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 12 months prior to screening~~

– if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Purpose: Clarify blinding language.

The changes occur in Section 3.5, Blinding.

Revised text: ~~All site~~**Site** personnel and patients will be blinded to study drug treatment**; site personnel preparing study drug may be unblinded to study drug treatment only where required by documented institutional procedure**.

…

All site personnel will be blinded to ~~central~~ laboratory results of oxalate, calcium oxalate supersaturation, and glycolate from after the time of the first dose until unblinding.

Purpose: Expand Inclusion Criterion 2 to allow ≥2 stone events with a minimum of 1 stone required in the 5 years prior to screening.

The primary change occurs in Section 4.1, Inclusion Criteria.

Revised text:

2. Recurrent kidney stone disease, defined as ≥2 stone events**, with a minimum of 1 stone event** within the 5 years prior to screening. For inclusion, a historical kidney stone event is defined as:
   - the visible passage of a kidney stone
   - a procedural intervention for removal of an asymptomatic or symptomatic stone
     – if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
     – if more than 1 procedure was required to remove a single stone, this counts as 1 event
   - a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging

     ~~– it must be evident from the CT scans that the new or enlarged kidney stone event occurred during 5 years prior to screening~~

– if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Section also reflecting this change:

- Protocol Synopsis

Purpose: Clarify the ULN for 24-hour urinary oxalate.

The change occurs in Section 4.1, Inclusion Criteria.

Revised text: 4. 24-hour urinary oxalate levels from 2 valid 24-hour urine collections obtained during screening are >ULN~~.~~ **(ULN = 40 mg/24 hours)**.

Purpose: Clarify that BMI in Inclusion Criterion 7 is at screening.

The change occurs in Section 4.1, Inclusion Criteria.

Revised text: 7. Body mass index (the weight in kilograms divided by the square of the height in meters) **at screening** of 20 to <40 kg/m^2.

Purpose: Remove eDiary modality.

The primary change occurs in Section 5.6.3, Dietary Restrictions.

Revised text: Dietary adherence will be collected ~~electronically in an eDiary~~**in a patient diary** at the time points listed in the Schedule of Assessments (Table 1). Refer to the Study Manual for more information.

Purpose: Remove electronic ICF option.

The primary change occurs in Section 6.1, Screening Assessments.

Revised text: An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed ~~(in paper or electronic format per local regulations and institutional standards)~~ by the patient before the screening procedures are initiated. All patients will be given a signed and dated version of their ICF.

Sections also reflecting this change:

- Section 8.1.1, Informed Consent

Purpose: Remove validity requirement for 24-hour urine sample prior to dosing and clarify patient procedures for providing samples.

The change occurs in Section 6.2.1, 24-Hour Urine Collection and Table 4: 24-hour Urine Collection Procedure by Study Visit.

Revised text: 2 valid collections prior to dosing unless variability criterion is not met (Section 6.2.1.2), in which case ~~3 valid collections are required~~**an additional collection is required**[a]

[a] **The additional collection is not required to be valid in order to proceed with dosing, but will be tested to confirm validity for the calculation of baseline 24-hour urinary oxalate.**

[ab] A supervised collection is defined, at a minimum, as contact from study staff to the patient the day prior to the collection start and the day the collection will finish to ensure compliance; this may be conducted remotely. Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine collection is not a supervised collection, or if a collection is supervised remotely, patients may either bring it to the clinic or have it couriered to the ~~designated laboratory.~~**clinic**

Section also reflecting this change:

- Table 1: Schedule of Assessments

Purpose: Clarify language regarding the collection of additional 24-hour urine samples.

The change occurs in Section 6.2.1.2, Variability Criterion for 24-hour Urine Collections at Screening

Revised text: If the variability is >20%, then ~~a third valid~~**an additional** 24-hour urine collection should be obtained. The result of the ~~third~~**additional** sample will not impact the patient's eligibility for the study.

Purpose: Removed all exploratory blood and urine samples including exploratory DNA assessments.

The primary change occurs in Section 6.3, Pharmacodynamic Assessments.

Revised text: Urine and blood samples will be collected for assessment of PD parameters (plasma oxalate~~,~~ **and** plasma glycolate, and urinary glycolate) at the time points specified in the Schedule of Assessments (Table 1). ~~Urine samples for exploratory analysis will be aliquoted from the samples provided for PD analysis.~~ On dosing days, all blood and urine samples will be collected prior to study drug administration.

Sections also reflecting this change:

- Table 1: Schedule of Assessments
- Section 6.6, ~~Biomarkers, Exploratory DNA Genotyping, and Biospecimen Repository~~ (removed)

Purpose: Remove urinalysis from clinical laboratory assessments.

The change occurs in Section 6.5.4, Clinical Laboratory Assessments and Table 5: Clinical Laboratory Assessments.

Removed text: ~~Urinalysis, Visual inspection for appearance and color, Bilirubin, pH (dipstick), Nitrite, Specific gravityRBCs, Ketones, Urobilinogen, Albumin, Leukocytes, Glucose, Microscopy (if clinically indicated), Protein~~

Purpose: Clarify blinding language.

The primary change occurs in Section 7, Statistics.

Revised text: A Statistical Analysis Plan (SAP) will be finalized before database lock~~ and study unblinding for the primary analysis~~. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

Section also reflecting this change:

- Section 7.2.11, Interim Analysis

Purpose: Added Plasma Oxalate Analysis Set in alignment with the study SAP; clarified language for the Safety Analysis Set.

The primary changes occur in Section 7.2.1, Populations to be Analyzed.

Revised text:

- **Plasma Oxalate Analysis Set: All patients who received at least 1 dose of study drug and have a baseline plasma oxalate level ≥1.5 times the lower limit of quantification/detection.**
- Safety Analysis Set: All~~ randomized~~ patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.

Sections also reflecting these changes:

- Protocol Synopsis
- Section 7.2.6, Pharmacodynamic Analysis

Purpose: Clarified language from MMRM model in alignment with the study SAP.

The primary change occurs in Section 7.2.5, Efficacy Analyses.

Revised text: The model includes baseline ~~value~~**24-hour urinary oxalate** and the stratification **factor** of number of historical kidney stone events (>1 versus ≤1 event in the 12 months prior to screening) as covariates, and fixed effect terms including treatment arm, visit and visit and treatment arm interaction.

Purpose: Remove 4 hour PK timepoint and clarify predose PK timepoint.

The change occurs in Table 2: Pharmacokinetic Time Points.

Purpose: Correct the provided formula for 2009 CKD-EPI equation for eGFR calculation.

The change occurs in Appendix 10.1, Formula for Estimated Glomerular Filtration Rate Calculation.

Revised text:

~~CKD-EPI (~~**Source:** Chronic Kidney Disease Epidemiology Collaboration~~).~~ **(CKD-EPI); Levey AS, Stevens LA, Schmid CH, et al.** A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009~~ May 5~~;150(9):604-~~12~~**612**.

- ~~Conventional units~~
- eGFR ~~(mL/~~**=** **141** × min~~/~~**(**S_{cr}**/κ,** 1~~.73m^2~~) = 175 × (SCr [mg/dL])~~$^-$~~**)**$^{\alpha}$ × **max(**S_{cr}**/κ,** 1~~$^{-.154}$~~ × (age)~~$^-$~~**)**$^{-1.209}$ × 0.~~^{203}~~ × (0.742, **993**^{Age} × **1.018 [**if female~~),~~**]** × **1.159 [if Black** 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)~~

  where:

  - **S_{cr} is serum creatinine in mg/dL**
  - **κ = 0.7 (females) or 0.9 (males)**
  - **α = -0.329 (female) or -0.411 (male)**
  - **min(S_{cr}/κ, 1) is the minimum of S_{cr}/κ or 1.0**
  - **max(S_{cr}/κ, 1) is the maximum of S_{cr}/κ or 1.0**
  - **Age (years)**

Abbreviations: eGFR= Estimated glomerular filtration rate; SCr=serum creatinine~~; SI=International System of Units~~

Administrative changes and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not listed individually.

CLINICAL STUDY PROTOCOL
ALN-GO1-008
DATED 24 JUNE 2021

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Short Title:	A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Study Drug:	Lumasiran (ALN-GO1)
EudraCT Number:	2021-001519-10
IND Number:	128941
Protocol Date:	Original protocol, 24 June 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	[redacted]

SPONSOR PROTOCOL APPROVAL

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

29 Jun 2021

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-008 protocol and agree to conduct the study in accordance with the protocol and all applicable regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Short Title

A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Study Drug

Lumasiran (ALN-GO1)

Phase

Phase 2

Study Centers

The study will be conducted at approximately 25 clinical study centers across Europe and the United States.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event

Objectives	Endpoints
• To evaluate additional pharmacodynamic (PD) parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize the pharmacokinetics (PK) of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on spot urinary oxalate:creatinine ratios	• Change from baseline in spot urinary oxalate:creatinine ratios
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
• To assess the impact of kidney stone events on patient-reported pain and quality of life (QoL)	• Patient-reported severity and symptomatic and functional impact of kidney stone events
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of adverse events (AEs)

Study Design

This is a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered subcutaneously (SC) in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to mean baseline urinary oxalate level and the number of kidney stone events in the 12 months prior to screening.

Number of Planned Patients

The planned enrollment for this study is 120 patients.

Diagnosis and Main Eligibility Criteria

This study will include adults (≥18 years of age) with a documented diagnosis of recurrent kidney stone disease based on ≥2 stone events within 5 years prior to screening. A historical clinical kidney stone event is defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on computed tomography (CT) imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 5 years prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

Study Drug, Dose, and Mode of Administration

Lumasiran (ALN-GO1) is a SC administered *N*-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA) targeting liver-expressed hydroxyacid oxidase (*HAO1*) messenger RNA (mRNA) for reduction of hepatic oxalate production.

Lumasiran will be administered by SC injection at a dose of 284 mg or 567 mg on Day 1, Month 3, and Month 9.

Reference Treatment, Dose, and Mode of Administration

Placebo (sodium chloride 0.9% w/v for SC administration) will be administered at the same dosing interval as lumasiran.

Duration of Treatment and Study Participation

The duration of treatment with study drug is up to 15 months. The estimated total time on study for each patient is up to 17 months, including up to 2 months of screening.

Statistical Methods

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05.

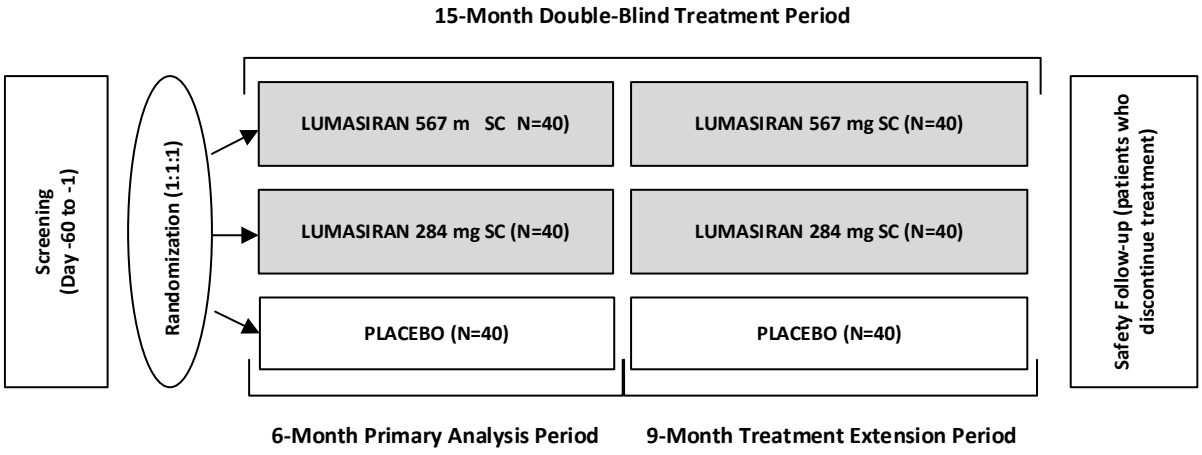
The populations (analysis sets) are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients who received at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Safety Analysis Set:** All randomized patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.
- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary efficacy endpoint will be analyzed in the FAS using a mixed-effect model for repeated measures (MMRM) approach. The primary comparison is percent change from baseline in urinary oxalate through Month 6.

Safety data will be summarized descriptively.

Figure 1: Study Design



Abbreviations: SC=subcutaneous(ly)

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]									Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period						Treatment Extension Period			
Study Visit			**Baseline**	**M2**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**57 (±7)**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**309 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Informed consent	Section 6.1	X										
Assign patient identification number	Section 3.4	X										
Demographics	Section 6.1	X										
Blood for DNA analysis	Unless tested previously, see Section 6.1.1	X										
Full physical examination	Section 6.5.3	X									X	
Follicle-stimulating hormone	To confirm post-menopausal status if applicable; Section 6.5.4.2	X										
Serum pregnancy test (for WOCBP)	See Section 6.5.4.2	X										

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]									Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period						Treatment Extension Period			
Study Visit			**Baseline**	**M2**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**57 (±7)**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**309 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
2 separate 24-hour urine collections	2 valid screening collections (see Section 6.2.1.1); a third collection may be required (see Section 6.2.1.1) Collect within 14 days prior to dosing (M9) or visit (M15); repeat if invalid. See Table 4	X							X		X	
Inclusion/exclusion criteria	Section 4.1; Section 4.2	X	X[b]									
Medical history	Section 6.1	X	X									
Height	Section 6.5.2	X	X								X	
Vital signs	Section 6.5.1	X	X		X				X		X	X
Body weight	Section 6.5.2	X	X		X				X		X	X
eDiary	Diet compliance check and 24-hour urine collection; Section 5.6.3	X			X	X	X	X	X		X	
Single 24-hour urine collection	Collect within 14 days prior to dosing (M3) or visit (M4, M5, M6); repeat if invalid. See Table 4				X	X	X	X				

Table 1: Schedule of Assessments

		Screening	15 Month Double-Blind Treatment Period[a]									Safety Follow-up (Patients who D/C Treatment Early)
			Primary Analysis Period						Treatment Extension Period			
Study Visit			**Baseline**	**M2**	**M3**	**M4**	**M5**	**M6**	**EOT M9**	**M12**	**EOS/ ET M15**	
Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**57 (±7)**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**309 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
Blood sample for PD analyses	Section 6.3	X	X		X			X	X		X	
Blood for exploratory analyses	Section 6.6	X	X		X			X	X		X	
Spot urine sample for PD and exploratory analyses	Single void collections for PD and exploratory analyses should be collected as a first morning void when possible; Section 6.3	X[c]	X[c]	X	X[c]	X	X	X[c]	X[c]	X	X[c]	X
Clinical laboratory assessments	Section 6.5.4	X	X		X			X	X		X	X
Antidrug antibody sample	Section 6.5.4.1		X		X			X	X		X	X
Urine pregnancy test (for WOCBP)[d]	May be performed more frequently where required per local requirements, or if pregnancy is suspected. See Section 6.5.4.2		X		X				X			
Symptom-directed physical examination	Section 6.5.3		X		X				X			X
Exploratory DNA sample (optional)	Section 6.6		X									

Table 1: Schedule of Assessments

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			Primary Analysis Period						Treatment Extension Period			
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Study Day (±Visit Window)	**Notes**	**-60 to -1**	**Day 1**	**57 (±7)**	**85 (±14)**	**113 (±7)**	**141 (±7)**	**169 (±14)**	**253 (±28)**	**309 (±7)**	**421 (±28)**	**3 and 6 months post last dose (±28)**
BPI-Short Form (Question 3 only)	Pain assessment, collected in an eDiary; Section 6.7.1	X	X	Continuous (at the time of a clinical kidney stone event)								
WISQOL	Collected in an eDiary; Section 6.7.2		X	Continuous (at the conclusion of a clinical kidney stone event)								
Prior and concomitant medications	Section 5.4	Continuous										
Clinical kidney stone events	Section 6.2.2	Continuous										
Review/record adverse events	Section 6.5.5	Continuous										
Healthcare utilization	Section 6.8	Continuous										
Randomization	Window: 1 business day prior to Day 1 for study drug preparation		X									
Study drug administration	Section 5.2.2		X		X				X			
Blood samples for PK analyses	Table 2; Section 6.4		X									
Low-dose kidney-protocol CT scan[e]	Section 6.2.2.2		X (-3 days window)								X	

Abbreviations: BPI=Brief Pain Inventory; CT=computed tomography; D/C=discontinue; DNA=deoxyribonucleic acid; ET=early termination; EOS=end of study; EOT=end of treatment; M=month; PD=pharmacodynamic; PK=pharmacokinetic; WISQOL=Wisconsin Stone Quality of Life Questionnaire; WOCBP=women of child-bearing potential

Notes:

- When scheduled at the same time points, assessments of vital signs should be performed before physical examinations and blood sample collections, where feasible.
- Patients who discontinue study drug dosing for any reason will be encouraged to remain on the study to complete the remaining assessments so that their experience is captured in the final analyses (refer to Section 4.3.1).
- White columns indicate visits to the clinical study center; gray-shaded columns indicate study visits that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion and with oversight of the Investigator, based on safety and tolerability), provided (for dosing visits) that the patient has tolerated a dose of lumasiran administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a symptom-directed physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications, kidney stone events, and adverse events.

Footnotes:

[a] **All assessments are required to be performed prior to dosing at dosing visits, except for the CT scan and PK sample collection.**

[b] Inclusion/exclusion criteria should be verified prior to randomization. Laboratory assessments conducted to confirm study eligibility will not be repeated unless the time between screening and randomization exceeds 4 weeks.

[c] Samples for exploratory analysis will only be collected at these visits and will be aliquoted from the samples provided for PD analysis.

[d] Pregnancy test results must be known prior to dosing, if applicable.

[e] May be performed after dosing, if required.

Table 2: Pharmacokinetic Time Points

Study Day	Sampling Time (hh:mm)	Blood PK Sample
Day 1	02:00 (±20 min)	X
	04:00 (±30 min)	X

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

- The hour (±range) indicates sample collection timing relative to dosing. Precise PK sample times (hour and minute) are recorded. Refer to Section 7.2.7 for additional information on PK assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum plasma concentration
CPC	Clinical product complaint
CT	Computed tomography
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
ESKD	End stage kidney disease
ET	Early termination
FAS	Full analysis set
GalNAc	*N*-acetylgalactosamine
GCP	Good Clinical Practice
GO	Glycolate oxidase
HAO1	Hydroxyacid oxidase 1
HED	Human equivalent dose
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection site reaction
LFT	Liver function test

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
mRNA	Messenger ribonucleic acid
PD	Pharmacodynamics
PH1/2/3	Primary hyperoxaluria type 1/2/3
PK	Pharmacokinetic
PT	Preferred term
QoL	Quality of life
RNAi	Ribonucleic acid interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization
WISQOL	Wisconsin Stone Quality of Life Questionnaire

1. INTRODUCTION

Alnylam Pharmaceuticals, Inc. (the Sponsor) has developed 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*) messenger ribonucleic acid (mRNA), blocking production of glycolate oxidase (GO) and hence reducing hepatic oxalate production.

Lumasiran is approved for the treatment of primary hyperoxaluria type 1 (PH1) in both pediatric and adult patients in the United States (23 November 2020) and in the European Union (19 November 2020). Based on lumasiran's mechanism of action, and demonstrated reduction of hepatic oxalate production in patients with PH1, the Sponsor is investigating whether treatment with lumasiran is effective for patients with recurrent calcium oxalate kidney stone disease who have elevated urinary oxalate levels but have not been diagnosed with PH1 or one of the other primary hyperoxalurias.

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

1.1. Study Rationale

Study ALN-GO1-008 is a randomized, double-blind, placebo-controlled, multi-center Phase 2 study designed to evaluate the efficacy, safety, pharmacodynamics (PD), and pharmacokinetics (PK) of lumasiran, administered subcutaneously (SC), in adult patients with recurrent calcium oxalate kidney stone disease.

The primary objective of the study is to evaluate the effect of lumasiran on the percent change in urinary oxalate excretion in patients with recurrent calcium oxalate kidney stones. Secondary and exploratory objectives of the study include the evaluation of the effect of lumasiran on urinary calcium oxalate supersaturation, the occurrence of kidney stones, the PD effect of lumasiran on plasma oxalate, plasma glycolate and urinary glycolate, and the characterization of plasma PK.

The full rationale for the study and design is presented in Section 3.2.

1.2. Background

Kidney stones are common, affecting approximately 1 in 11 people in the United States, and the prevalence of kidney stone disease has been increasing worldwide over time.[Scales 2012] Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals, with the remainder being predominantly calcium phosphate, uric acid, cystine, or struvite.[Worcester and Coe 2008; Worcester and Coe 2010] Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine (Figure 2). High levels of urinary oxalate may be derived from both endogenous synthesis and diet.

Kidney stones can develop in patients of all ages; however, the highest incidence rates occur in individuals aged 40 to 66 years.[Shin 2018] There is significant clinical burden associated with the development of kidney stones for patients with recurrent calcium oxalate kidney stone disease, including pain, infection/sepsis, diagnostic and therapeutic procedures, hospitalizations,

and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease (ESKD).

The typical clinical presentation of kidney stones includes sudden onset of lumbar flank pain and hematuria, and may include nausea and vomiting. Evaluation to assess etiology includes assessment of the patient's medical history, medication use, and dietary and lifestyle risk factors. Confirmation of diagnosis may involve renal ultrasound, abdominal x-ray, and/or computed tomography (CT).[Heilberg and Schor 2006] 24-hour urine collections analyzed for total volume, calcium, oxalate, uric acid, citrate, and other analytes may help to determine the underlying etiology.[Pearle 2014] Stone composition is generally determined in at least one instance.

There are limited effective treatment options for patients with recurrent calcium oxalate kidney stone disease. Preventive measures in American and European guidelines recommend adequate fluid intake to ensure a urine volume of at least 2 to 2.5 liters daily and provide dietary advice to limit the consumption of oxalate-rich foods, sodium chloride, and animal protein content, while maintaining a normal calcium intake. In some situations, thiazide diuretics, potassium citrate, and/or allopurinol may be considered.[Pearle 2014; Türk 2021]

Treatment of pain associated with kidney stone events may involve non-steroidal anti-inflammatory agents and/or opiate pain medications. Depending on the clinical context, medical expulsive therapy, extracorporeal shock-wave lithotripsy, ureteroscopy, stenting, and percutaneous nephrolithotomy are some of the treatment options that may be pursued.[Türk 2021]

Lumasiran is a ribonucleic acid interference (RNAi) therapeutic designed to reduce hepatic oxalate production. Oxalate produced by the liver is largely excreted in the urine, and lumasiran has been shown to reduce urinary oxalate in patients with PH1. High levels of urinary oxalate increase the risk of stone formation; therefore, lumasiran may have efficacy in patients with recurrent calcium oxalate kidney stone disease who do not have PH1 but who produce high amounts of oxalate endogenously.

1.3. Benefit-Risk Assessment

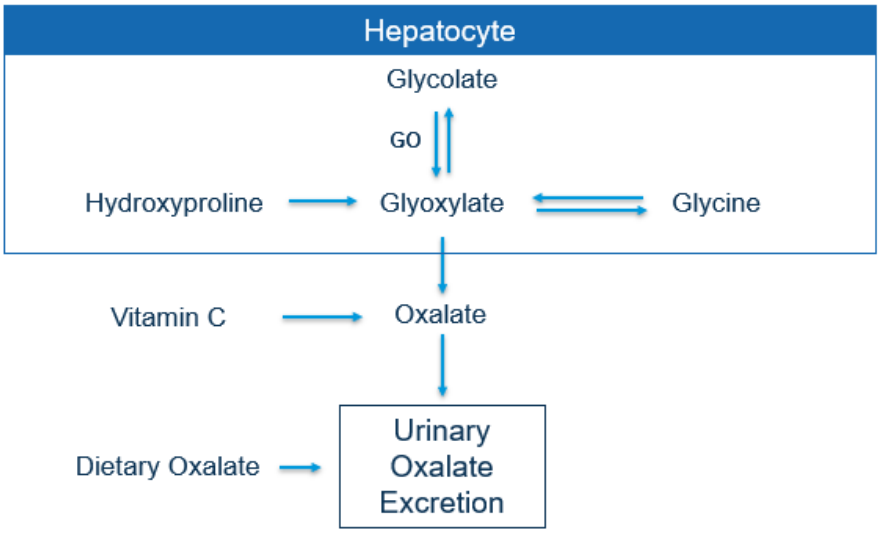
Calcium oxalate stone formation occurs when a supersaturating level of calcium oxalate is present in the urine, with increasing risk of stone formation as urine oxalate levels increase.[Curhan and Taylor 2008] More than half of oxalate is endogenous in origin and presumed to come largely from the liver.[Mitchell 2018] Studies have shown that reduced calcium oxalate supersaturation and urinary oxalate levels are associated with reduced stone formation.[Borghi 2002; Ferraro 2018; Prochaska 2018]

For patients with recurrent calcium oxalate stone formation, multiple stone removal procedures may be required. These procedures are invasive and place the patient at risk of complications including bleeding and infection. Patients experiencing obstructive kidney stones can also experience acute kidney injury with permanent loss of renal function. As a result, patients with recurrent kidney stone formation have a higher risk of progression to CKD and ESKD.[Dhondup 2018; Rule 2009]

Lumasiran, approved in the United States and European Union for the treatment of PH1, is designed to reduce hepatic production of oxalate. Based on the available data from clinical and

nonclinical studies, lumasiran, administered SC, demonstrated a potent, dose-dependent inhibition of GO resulting in decreased urinary and plasma oxalate and increased plasma and urinary glycolate. Lumasiran may be effective in lowering urinary oxalate levels in patients with recurrent calcium oxalate kidney stone disease (Figure 2). No adverse effects of elevated glycolate have been reported. Unlike oxalate, glycolate is highly soluble and readily excreted in the urine.

Figure 2: Summary of Endogenous Oxalate Synthesis



Abbreviations: GO=glycolate oxidase

Lumasiran has been well tolerated with an acceptable safety profile in studies with healthy volunteers and patients with PH1. Most adverse events (AEs) have been mild or moderate in severity. Transient, mild injection site reactions (ISRs) have been observed. No clinically significant laboratory changes related to lumasiran 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 hepatic effects. The study has specific 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 (LFTs). As the risk of embryofetal toxicity in humans is currently unknown, females who are of child-bearing potential during the study must have a negative pregnancy test, cannot be breast feeding, and must be willing to use contraception as specified in the protocol (see Section 5.6.1).

Based on the available efficacy and safety data from clinical and nonclinical studies, the benefit-risk assessment supports the evaluation of lumasiran in a Phase 2 study in patients with recurrent calcium oxalate kidney stone disease.

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

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event
• To evaluate additional PD parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize PK of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on spot urinary oxalate:creatinine ratios	• Change from baseline in spot urinary oxalate:creatinine ratios
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time

Objectives	Endpoints
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
• To assess the impact of kidney stone events on patient-reported pain and quality of life (QoL)	• Patient-reported severity and symptomatic and functional impact of kidney stone events
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of AEs

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a randomized, placebo-controlled, double-blind, multicenter, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered SC in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels (Figure 1).

The study will consist of up to 2 months of screening and 15 months of double-blind treatment (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period). Patients will be screened from Day -60 to Day -1 to determine eligibility. During screening, patients will provide at least two 24-hour urine collections to establish baseline urinary oxalate levels. Consented patients meeting all eligibility criteria will be randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo. Stratification will be performed at randomization according to mean baseline urinary oxalate level and the number of kidney stone events in the 12 months prior to screening as discussed in Section 3.4.

During the 6-month Primary Analysis Period, patients will be dosed on Day 1 (baseline) and at Month 3. During the Treatment Extension Period, one additional dose will be administered at Month 9; an end of study (EOS) visit will take place at Month 15. Study drug will be administered SC as specified in Section 5.2.2. Patients will be assessed for efficacy, safety, PD, and PK according to the Schedule of Assessments (Table 1 and Table 2). Efficacy assessments will include evaluation of urinary oxalate excretion, urinary calcium oxalate supersaturation, and kidney stone events (including clinical events and low-dose kidney-protocol CT). Safety assessments will include collection of AEs, clinical laboratory tests, vital sign assessments, physical examinations, and concomitant medications.

Patients who discontinue study drug early will be asked to return for follow-up visits as described in Section 4.3.1.

3.2. Scientific Rationale for Study Design

The primary endpoint for this Phase 2 study is the percent change in 24-hour urinary oxalate excretion. To confirm the optimal dosing regimen, and to facilitate the collection of kidney stone event data (an exploratory endpoint), the study will continue through Month 15. A placebo comparator is included because there is no approved standard of care therapy to decrease urinary oxalate.

A blood DNA sample will be collected as part of standard screening assessments (if testing has not already been performed) to ensure the exclusion of patients with primary hyperoxaluria type 1 (PH1), type 2 (PH2), and type 3 (PH3). Lumasiran is approved in some countries for the treatment of PH1, and patients with PH2 and PH3 are not expected to respond to lumasiran.

Because the primary endpoint will rely on measurements of urinary oxalate, and because some urinary oxalate is diet-derived, diet is an important variable in this study. In a 5-year study of recurrent stone formers published by Borghi et al, patients randomized to a normal calcium, low protein/salt diet had lower urinary oxalate levels and a lower cumulative incidence of recurrent kidney stones when compared to a low calcium diet. During the current study, and as of the time of informed consent, patients will be asked to adhere to a diet appropriate for stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate.

The secondary endpoint to assess meaningful reduction in 24-hour urinary oxalate from baseline to Month 6 (Months 4 through 6) defines a clinically meaningful reduction as ≥20% in the non-PH1 stone former population, supported by available literature based on stone former populations.[Borghi 2002]

In this study, lumasiran will be evaluated in patients with recurrent calcium oxalate kidney stone disease. Due to the limited and burdensome disease management options, there is an unmet need for new therapies.

3.3. Justification for Dose

Two dose levels of lumasiran 284 and 567 mg given on Day 1, Month 3, and Month 9 were selected to evaluate urinary oxalate dose response. The higher dose level of 567 mg is expected to suppress GO enzyme by ≥95%, comparable to the regimen evaluated in ALN-GO1-003 (ILLUMINATE-A) in patients with PH1. The lower dose of 284 mg is expected to suppress GO enzyme by 90%. In addition, the fixed doses will simplify dose administration in this adult study population. Both regimens are predicted to achieve near-steady state ribonucleic acid-induced silencing complex (RISC) concentrations and urinary oxalate suppression at Month 6. Month 9 dosing is intended to sustain PD effect through Month 15 and will provide data to differentiate the effect of every 3 months and every 6 months dosing on urinary oxalate reduction.

Single 0.3 to 6.0 mg/kg doses of lumasiran in healthy subjects and multiple 3.0 mg/kg doses of lumasiran administered monthly or once every 3 months in patients with PH1 have been well tolerated. Plasma and liver exposure for the lumasiran 284 and 567 mg doses are expected to be in the range of 3.0 to 6.0 mg/kg lumasiran doses evaluated in healthy subjects in ALN-GO1-001

(Part A) and patients with PH1 in ALN-GO1-001 (Part B), ALN-GO1-002, and ILLUMINATE-A. Based on rat and monkey NOAEL doses of lumasiran 200 mg/kg and 300 mg/kg, a sufficient safety margin exists for the use of lumasiran 284 and 567 mg doses (refer to the ALN-GO1 Investigator Brochure).

Based on a 70 kg patient, the planned doses of 284 mg and 567 mg equate to approximately 4.0 mg/kg or 8.0 mg/kg, respectively. The human equivalent dose (HED) margin values for the approximate 4 mg/kg clinical dose were 8.1-fold for the chronic rat study and 24.2-fold for the chronic monkey study; the HED margin values for the approximate 8.0 mg/kg clinical dose were 4.0-fold for the chronic rat study and 12.1-fold for the chronic monkey study (refer to the ALN-GO1 Investigator Brochure).

3.4. Method of Assigning Patients to Treatment Groups

Each patient will be uniquely identified in the study by a combination of the site number and patient identification number. After the patient signs the informed consent form (ICF) and before proceeding with screening procedures, the Investigator or his/her designee will contact the Interactive Response Technology (IRT) to obtain a patient identification number.

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

Patients will be randomized 1:1:1 to receive lumasiran 284 mg, lumasiran 567 mg, or placebo, administered at the same volume (see Section 5.2.2), for the duration of the study. Stratification will be performed at randomization according to mean baseline urinary oxalate level (>1.25 × ULN vs ≤1.25 × ULN) and the number of historical kidney stone events in the 12 months prior to screening (>1 vs ≤1).

For stratification, a historical kidney stone event is defined as:

- the visible passage of a kidney stone
- a procedural intervention for removal of an asymptomatic or symptomatic stone
  - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
  - if more than 1 procedure was required to remove a single stone, this counts as 1 event
- a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
  - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during the 12 months prior to screening
  - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.

3.5. Blinding

All site personnel and patients will be blinded to study drug treatment. The Sponsor will have access to unblinded study data during the conduct of the study. Lumasiran and placebo will be

packaged identically and will be administered at the same volume under the supervision of the Investigator at the study center or by a healthcare professional at the patient's home (see Section 5.2.2). Since lumasiran may be visually distinguishable from placebo, the syringe will be masked prior to administration by a healthcare professional. See the Pharmacy Manual for additional details.

All site personnel will be blinded to central laboratory results of oxalate, calcium oxalate supersaturation, and glycolate from after the time of the first dose until unblinding. Results will not be reported to the Investigator from the first dose until the last patient completes assessments at the Month 15 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 measurements for oxalate, calcium oxalate supersaturation, or glycolate from the first dose until the sites and patients are unblinded, or until the patient ends the study, whichever is earlier. If oxalate, calcium oxalate supersaturation, or glycolate are 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.

Any unplanned unblinding occurring during the study period will be documented and reported in the clinical study report.

3.5.1. 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. If contact prior to unblinding is not possible, personnel must contact the Medical Monitor 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 trial master file.

Refer to the IRT instructions for details on unblinding.

3.6. Safety Review

A safety review committee will not be utilized for this study; however, the Sponsor will monitor safety on an ongoing basis and in accordance with the Sponsor's internal processes.

3.7. Definition of End of Study for an Individual Patient

A patient is considered to have reached the EOS if the patient:

- has completed the EOS (Month 15) visit, or
- has completed safety monitoring following the final dose of study drug as described in Section 4.3.1

A definition of the end of the overall study is provided in Section 8.1.5.

4. SELECTION AND REMOVAL OF PATIENTS

4.1. Inclusion Criteria

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

Age

1. Age 18 years or older (or age of legal consent, whichever is older).

Patient and Disease Characteristics

2. Recurrent kidney stone disease, defined as ≥2 stone events within the 5 years prior to screening. For inclusion, a historical kidney stone event is defined as:
   - the visible passage of a kidney stone
   - a procedural intervention for removal of an asymptomatic or symptomatic stone
     - if more than 1 stone was removed in a given procedure, this counts as 1 event unless bilateral ureteral stones were removed, in which case this counts as 2 events
     - if more than 1 procedure was required to remove a single stone, this counts as 1 event
   - a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone on CT imaging
     - it must be evident from the CT scans that the new or enlarged kidney stone event occurred during 5 years prior to screening
     - if a procedure was performed to remove the stone(s) identified by CT, then only the procedure will be counted to avoid double-counting the same stone.
3. The 2 most recently analyzed kidney stones prior to randomization contained 50% or more of calcium oxalate; if only one stone analysis is available, then it must have contained 50% or more of calcium oxalate.
4. 24-hour urinary oxalate levels from 2 valid 24-hour urine collections obtained during screening are >ULN.
5. Willing to adhere to dietary recommendations appropriate for stone formers including limiting vitamin C supplementation to <200 mg daily.
6. If taking medications and/or hydrating for kidney stone prophylaxis, or taking medications that alter urinary oxalate excretion and/or kidney stone formation, must have been on a stable regimen for at least 60 days before randomization, and willing to remain on this stable regimen for the duration of the study.
7. Body mass index (the weight in kilograms divided by the square of the height in meters) of 20 to <40 kg/m^2.

Informed Consent

8. Patient is able to understand and is willing and able to comply with the study requirements and to provide written informed consent.

4.2. Exclusion Criteria

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

Laboratory Assessments

1. Has any of the following laboratory parameter assessments at screening:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN
    b. Total bilirubin >1.5 × ULN. Patients with elevated total bilirubin that is secondary to documented Gilbert's syndrome are eligible if the total bilirubin is <2 × ULN
    c. International normalized ratio (INR) >2.0 (patients on oral anticoagulant [eg, warfarin] with an INR <3.5 will be allowed)
2. Has an eGFR of <30 mL/min/1.73m^2 at screening (calculation will be based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine formula; see Section 10.1).

Prior/Concomitant Therapy

3. Received an investigational agent within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug, or are in follow-up of another clinical study prior to study enrollment. Any agent that has received health agency authorization (including for emergency use) by local or regional regulatory authorities is not considered investigational.

Medical Conditions

4. Patients with a known history of secondary causes of elevated urinary oxalate and/or recurrent kidney stones including:
    a. Primary hyperoxaluria
    b. Severe eating disorders (anorexia or bulimia)
    c. Chronic inflammatory bowel disease
    d. Intestinal surgery with malabsorption or chronic diarrhea
    e. Sarcoidosis
    f. Primary hyperparathyroidism
    g. Complete distal renal tubular acidosis
5. Has other medical conditions or comorbidities which, in the opinion of the Investigator, would interfere with study compliance or data interpretation.
6. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
7. History of intolerance to SC injection(s).

Contraception, Pregnancy, and Breastfeeding

8. Is not willing to comply with the contraceptive requirements during the study period, as described in Section 5.6.1.
9. Female patient is pregnant, planning a pregnancy, or breast-feeding.

Alcohol Use

10. 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]).
11. History of alcohol abuse, within the last 12 months before screening, in the opinion of the Investigator.

4.3. Removal from Study Drug or Assessment

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

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

4.3.1. Discontinuation of Study Drug or Declining Procedural Assessments

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

- Significant protocol deviation
- Adverse event
- Non-adherence to treatment regimen
- Pregnancy
- Lost to follow-up
- Other reason (non-AE)
- Or, study is terminated by the Sponsor

If possible, the Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from study drug dosing immediately (see Section 6.5.5.7 for reporting and follow-up of pregnancy). A positive urine pregnancy test should be confirmed by a serum pregnancy test prior to discontinuing the study drug.

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

If this occurs, the Investigator is to discuss with the patient the appropriate processes for discontinuation from study drug and must discuss with the patient the options for continuation of

the Schedule of Assessments (Table 1), including different options for follow-up and collection of data (eg, in person, by phone, by mail, or from options not involving patient contact, such as communication with other treating physicians or from review of medical records), including endpoints and AEs, and must document this decision in the patient's medical records.

If a patient discontinues dosing due to an AE, including serious adverse events (SAEs), the event should be followed as described in Section 6.5.5. When a patient discontinues study drug dosing, the primary reason must be recorded in the eCRF. Patients who discontinue study drug and remain on study may receive treatment consistent with local standard practice for their disease per Investigator judgement, as applicable.

Patients who discontinue from study drug during the 6-month Primary Analysis Period (defined as a discontinuation that occurs after the first dose of study drug administration on Day 1 during the 6-month Primary Analysis Period) will be encouraged to remain on the study and complete all assessments (including 24-hour urine collections) through Month 6, with early termination (ET) assessments at Month 9, and safety follow-up per the safety follow-up schedule (Table 1). Patients who do not remain on the study through Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete safety follow-up per the safety follow-up schedule (Table 1).

Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete ET assessments and complete a safety follow-up visit per the safety follow-up schedule (see Table 1).

4.3.2. Stopping a Patient's Study Participation

4.3.2.1. Patient Stops Participation in the Study

A patient may stop participation in the study at any time. A patient considering stopping participation in the study should be informed that the patient can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in Section 4.3.1. If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the ET assessments (see Table 1).

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

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

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

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

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

The Investigator or Sponsor may stop the participation of a patient in the study at any time if this is considered to be in the patient's best interest. However, study integrity and interpretation are best maintained if all enrolled patients continue study assessments through the Primary Analysis Period (Month 6).

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

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

The primary reason that a patient's study participation is stopped must be recorded in the appropriate section of the eCRF and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient's study participation is stopped due to an AE, including SAEs, the event should be followed as described in Section 6.5.5.

4.3.3. Lost to Follow-Up

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center. The following actions must be taken if a patient 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 continue in the study, and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (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.

- For patients who are lost to follow-up, the Investigator can search publicly available records (where permitted and allowed by local law) to ascertain survival status. This ensures that the outcome of the study is as comprehensive as possible.

4.3.4. Replacement of Study Patients

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

5. TREATMENTS AND OTHER REQUIREMENTS

5.1. Treatments Administered

Study drug (lumasiran and placebo) 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 study drug 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

Patients will be administered SC injections of lumasiran (284 mg or 567 mg) and/or placebo at the same volume, as described below, on Day 1, Month 3, and Month 9.

Lumasiran 567 mg	**Lumasiran 284 mg**	**Placebo**
1.5 mL lumasiran 1.5 mL lumasiran	1.5 mL lumasiran 1.5 mL placebo	1.5 mL placebo 1.5 mL placebo

Study drug injections will be administered under the supervision of the Investigator or healthcare professional. To maintain the blind, syringes are to be masked prior to the removal of study drug from vials. A full description of the blinding procedure is included in the Pharmacy Manual. The injection site may be marked and mapped for later observation. Injections may be administered in the abdomen, thigh, or the side or back of the upper arms. If a local reaction around the injection site occurs, photographs may be obtained. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be permitted at a location other than the study center (for example, the patient's home) by a healthcare professional with the oversight of the Investigator, provided the patient has tolerated at least 1 dose of study drug administered in the clinic. However, continued study

drug administration at the study center should be considered for patients who have ongoing study drug-related AEs 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 visit window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

Additional details can be found in the Pharmacy Manual.

The definition of study drug overdose, follow-up procedures, and reporting requirements are provided Section 6.5.5.8.

5.2.3. Dose Modifications

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. Results of previous LFT assessment 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 3.
3. For any ALT or AST elevation >3× ULN:
    a. If local laboratory results are obtained, confirm with a 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 5 and Table 6.
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 3.

Table 3: 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least every 2 weeks: LFT per Table 5 • 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 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 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. • Evaluate the initial elevation in LFT per the following assessments until satisfactory resolution: – Table 6 (all assessments to be performed once) – Hematology, serum chemistry, and LFT per Table 5 – Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) • Monitor at least weekly: LFT per Table 5 until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; 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. Clinical Product Complaints

5.3.1. Definition

A clinical product complaint (CPC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the study drug and its packaging after it is released for distribution to the site at which study drug will be administered.

A CPC may be detected prior to use of study drug, during use, or after use. A CPC is typically non-medical in nature; however, it is possible that investigational product complaints could be associated with an AE. Examples of a CPC include, but are not limited to: illegible clinical label, missing clinical label, damaged vial, empty vial, and contamination of study drug.

5.3.2. Reporting

For CPCs, the Sponsor or its designee should be notified within 24 hours using the appropriate eCRF. Clinical product complaints that may be associated with an AE must be evaluated and reported as indicated in Section 6.5.5. Detailed instructions on reporting CPCs will be provided in the Pharmacy Manual.

5.4. Concomitant Medications and Procedures

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

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

Standard vitamins and topical medications are permitted (vitamin C supplementation must be <200 mg daily per inclusion criteria). However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated.

Patients will be allowed to receive vaccines (eg, for SARS-CoV-2) that have received health agency authorization (including for emergency use) by local or regional regulatory authorities.

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.

5.5. Treatment Compliance

Compliance with study drug administration will be verified through observation by study staff or trained home healthcare professionals.

5.6. Other Requirements

5.6.1. Contraception

Females of child-bearing potential must be willing to use an acceptable method of contraception from 14 days before first dose, throughout study participation, and for 6 months after last dose administration or until study completion.

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 (except low-dose gestagens), implantable, injectable, or transdermal hormonal methods of contraception associated with the inhibition of ovulation.
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients must agree to use one of the above-mentioned contraceptive methods if they start heterosexual relationships during the study and for up to 6 months after the last dose of study drug.

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

Females of child-bearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause, confirmed by a 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, in order to comply with local requirements as described in the corresponding patient ICFs.

Compliance with contraception requirements will be assessed on a regular basis by the Investigator throughout the course of the study (see Section 6.5.4.2).

5.6.2. 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.

5.6.3. Dietary Restrictions

For the duration of the study patients should adhere to a diet appropriate for calcium oxalate stone formers, including adequate calcium intake and avoidance of spinach and other foods that are high in oxalate. Details are provided in the Dietary Reference Sheet.

Dietary adherence will be collected electronically in an eDiary at the time points listed in the Schedule of Assessments (Table 1). Refer to the Study Manual for more information.

6. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1. All assessments are required to be performed prior to dosing at dosing visits, except for CT imaging and PK postdose sample collection. Additional information on the collection of study assessments will be detailed in the Study Manual.

Where applicable country and local regulations and infrastructure for home healthcare allow, and as noted in Table 1, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include pregnancy testing (urine or serum), clinical laboratory assessments, urine collections, DNA testing, symptom-directed physical examination / body system assessment, vital signs, body weight, height, blood collection for PD, ADA and exploratory analyses assessments (at the discretion and with oversight of the Investigator).

6.1. Screening Assessments

An ICF that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be signed (in paper or electronic format per local regulations and institutional standards) by the patient before the screening procedures are initiated. All patients will be given a signed and dated version of their ICF.

Patients will be screened to ensure that they meet all the inclusion criteria and none of the exclusion criteria. To confirm study entrance criteria, 24-hour urine will be collected per Table 4.

Patient demographic data and medical history/disease history will be obtained. Any changes to medical history occurring between the screening assessment and prior to dosing will be updated.

6.1.1. DNA Sample

A blood sample for DNA analysis will be collected from all patients as part of the screening assessments. The samples will be analyzed for PH1, PH2, and PH3 (unless tested previously) to confirm eligibility (see Section 4.2). Refer to the Laboratory Manual for more information.

6.1.2. Retesting

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

6.1.3. Rescreening

Rescreening of patients is permitted with approval of the Medical Monitor. 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 be allowed to return for rescreening. A patient will be re-consented if rescreening occurs outside of the 60-day screening window. In this case, all screening procedures must be repeated.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to treatment with study drug. The site should update the patient's status in the IRT to reflect this as soon as possible.

6.2. Efficacy Assessments

Efficacy assessments are to be performed as specified in the Schedule of Assessments (Table 1).

6.2.1. 24-Hour Urine Collections

Urinary oxalate excretion and calcium oxalate supersaturation (calculated from multiple parameters) will be determined from 24-hour urine sample collections to be completed at the time points specified in the Schedule of Assessment (Table 1). The start and stop dates/times of collection, the volume of urine in the collection, whether there were any missed voids, and whether the patient complied with dietary recommendations will be recorded. An aliquot of the 24-hour urine collection will also be used to determine urinary creatinine content and to determine if the 24-hour urine collections need to be repeated (see Section 6.2.1.1).

The 24-hour urine collection procedure by study visit is provided in Table 4.

Table 4: 24-hour Urine Collection Procedure by Study Visit

Study Visit and Urine Collection Window	**Number of Collections to Schedule**	**Validity Requirement Prior to Dosing/Visit** (see Section 6.2.1.1)	**Notes**
Screening (within 60-day period)	2	2 valid collections prior to dosing unless variability criterion is not met (Section 6.2.1.1), in which case 3 valid collections are required.	Supervised collections[a] are encouraged unless patient is already familiar with the collection procedure. If any collections are invalid, the remaining collections for screening must be supervised.
Months 3, 4, 5, and 6 (within 14 days prior to dosing/visit)	1	No	If an invalid collection is obtained for the timepoint, a single repeat collection must be supervised. Repeat collection, if necessary, is to be completed within ±14 days of dosing/visit.
Months 9 and 15 (within 14 days prior to dosing/visit)	2	1 valid collection prior to dosing/visit	If a patient has had ≥2 prior invalid collections, both collections at these visits must be supervised[a]. At least 1 valid collection must be obtained prior to dosing/visit. If any collections for the timepoint are invalid, the remaining collection(s) for the timepoint must be supervised.

[a] A supervised collection is defined, at a minimum, as contact from study staff to the patient the day prior to the collection start and the day the collection will finish to ensure compliance; this may be conducted remotely. Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine collection is not a supervised collection, or if a collection is supervised remotely, patients may either bring it to the clinic or have it couriered to the designated laboratory.

6.2.1.1. Validity Criteria for 24-hour Urine Collections

Throughout the study, a urine collection will be considered valid if each of the following criteria are met:

- The collection is between 22 to 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.
- Patient complied with dietary recommendations appropriate for oxalate stone formers (detailed in the Dietary Reference Sheet) for the 4 days prior to the start of the urine collection and during the collection.

24-hour urine collections that are known to be invalid should still be submitted for analysis.

6.2.1.2. Variability Criterion for 24-hour Urine Collections at Screening

If the 2 valid 24-hour urine collections from screening meet eligibility requirements (both 24-hour urinary oxalate levels >ULN), the variability between the oxalate levels (in mg/day) should be assessed as follows:

$$Variability = \left|\frac{(Oxalate\ value\ \#1 - Oxalate\ value\ \#2)}{(Average\ of\ oxalate\ values\ \#1\ \&\ \#2)}\right| \times 100\%$$

If the variability is >20%, then a third valid 24-hour urine collection should be obtained. The result of the third sample will not impact the patient's eligibility for the study.

6.2.2. Kidney Stone Events

Since kidney stone events are recorded as an efficacy assessment, these events will not be captured as AEs or SAEs. However, if a patient experiences other AEs or SAEs during a kidney stone event, they should be reported as an AE (see Section 6.5.5.2).

Kidney stone events will be graded by the Investigator as mild, moderate, or severe as defined in Section 6.5.5.1. If there are changes in grade during an event, only the highest grade should be reported.

6.2.2.1. Clinical

All relevant clinical information pertaining to a kidney stone events should be obtained, including laboratory values, medical records, discharge summaries, and medical test results (including stone composition, if available, and radiology reports). A clinical kidney stone event is defined as one of the following:

- Visible passage of a kidney stone
- A procedural intervention for removal of an asymptomatic or symptomatic stone (information on the location, number, and size of stones removed will be collected)

- Or, in the case of potential stone passages without visible stones, it will be up to the Investigator to evaluate patients' symptoms and determine whether a stone passage occurred or the symptoms were due to a different cause.

6.2.2.2. Radiographic

A non-contrast low-dose kidney-protocol CT scan will be performed for all patients on Day 1 (may be performed up to 3 days prior to Day 1), and at Month 15.

For patients who terminate the study early, a CT scan should be performed at the ET visit only if this visit occurs after Month 6 and at the discretion of the Investigator, and where permitted, following consultation with the Medical Monitor. CT scans will be analyzed centrally.

6.2.3. Spot Urinary Oxalate:Creatinine Ratios

Urine oxalate:creatinine ratios will be calculated from the oxalate and creatinine levels measured in single-void urine collections. Single-void urine collections should be collected as a first morning void when possible; if this is not possible then the reason should be documented.

6.2.4. Estimated Glomerular Filtration Rate

Blood samples for the assessment of eGFR (mL/min/1.73m^2) will be obtained at the time points specified in the Schedule of Assessment (Table 1).

eGFR will be calculated based on the CKD-EPI formula (see Section 10.1).[Levey 2009; Schwartz 2009]

6.3. Pharmacodynamic Assessments

Urine and blood samples will be collected for assessment of PD parameters (plasma oxalate, plasma glycolate, and urinary glycolate) at the time points specified in the Schedule of Assessments (Table 1). Urine samples for exploratory analysis will be aliquoted from the samples provided for PD analysis. On dosing days, all blood and urine samples will be collected prior to study drug administration.

All PD assessments will be analyzed centrally. Postdose PD results will not be distributed to the sites until after the last patient completes assessments at the Month 15 visit. Site personnel should refrain from obtaining or viewing local oxalate, calcium oxalate supersaturation, or glycolate assessments, except as medically indicated, due to risk of unblinding (Section 3.5). Details regarding the processing and aliquoting of PD samples for shipping and storage are provided in the Laboratory Manual.

Where local regulations allow and infrastructure is in place, a healthcare professional may collect urine or blood samples offsite.

6.4. Pharmacokinetic Assessments

Blood samples will be collected for the assessment of lumasiran PK parameters at the time points indicated in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 2.

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

6.5. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication and measurements of vital signs, weight and height, and laboratory tests. Clinically significant abnormalities observed during the physical examination are recorded as either medical history or AEs, as appropriate.

Safety assessments are to be performed as specified in the Schedule of Assessments (Table 1). On dosing days and as applicable, assessments of vital signs, weight/height, physical examination, and clinical laboratory assessments are to be completed before study drug administration.

Adverse event assessments are detailed under Section 6.5.5.

6.5.1. Vital Signs

Vital signs will be measured as specified in the Schedule of Assessments (Table 1) and include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured predose, when applicable. 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 predose in the seated or supine position, after the patient has rested comfortably for approximately 5 minutes. Blood pressure should be taken using the same arm when feasible. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

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

Vital signs results will be recorded in the eCRF.

6.5.2. Height and Weight

Height will be measured in centimeters. Body weight will be measured in kilograms. Height and body weight measurements will be collected as specified in the Schedule of Assessments (Table 1) and will be recorded in the eCRF.

6.5.3. Physical Examination

Full and symptom-directed physical examinations will be conducted according to the Schedule of Assessments (Table 1); 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. If a visit is conducted offsite (eg, home), a body system assessment may be performed in lieu of a physical examination.

Symptom-directed physical examinations will be guided by evaluation of ongoing symptoms, changes in symptoms, or the onset of new symptoms, since the last visit. If there are no ongoing symptoms, changes in symptoms, or new symptoms, then a symptom-directed physical examination is not required.

Clinically significant abnormalities observed during the physical examination are recorded on the medical history eCRF (if observed during screening) or the AE eCRF (if observed at any post-screening visit).

6.5.4. 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. Laboratory assessments conducted to confirm study eligibility (Section 4) will not be repeated unless the time between screening and randomization exceeds 4 weeks. 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, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor; results may be collected and included in the clinical database. Clinical laboratory assessments are listed in Table 5 and will be assessed as specified in the Schedule of Assessments (see Table 1).

While local laboratory results may be used for urgent clinical decisions, on the day of visit assessments, all laboratory assessments specified in Table 5 which are performed at a local laboratory should also be sent in parallel to the central laboratory. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results on samples drawn on the same day.

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 5: Clinical Laboratory Assessments

Hematology	
Complete blood count with differential	
Serum Chemistry	
Sodium	Potassium
BUN	Albumin
Total protein	Calcium
Glucose	Bicarbonate
Creatinine and eGFR[a]	Chloride
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	
International Normalized Ratio (screening only)	
Immunogenicity (see Section 6.5.4.1)	
Antidrug antibodies	
Pregnancy Testing/FSH Screening (see Section 6.5.4.2)	
β-human chorionic gonadotropin (females of child-bearing potential only)	Follicle-stimulating hormone (postmenopausal women only)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; RBCs=red blood cells

[a] Refer to Section 10.1 and the laboratory manual for further instructions on calculating eGFR.

6.5.4.1. Immunogenicity

Blood samples will be collected to evaluate ADA. Blood samples for ADA testing must be collected before study drug administration as specified in the Schedule of Assessments (Table 1).

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

6.5.4.2. Pregnancy Testing

A pregnancy test will be performed for females of child-bearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed thereafter per the Schedule 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 that is 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 6.5.5.7 for follow-up instructions).

A blood sample will be drawn at screening to measure the levels of follicle stimulating hormone in order to confirm post-menopausal status in all women suspected to be post-menopausal. Post-menopausal women and women who are permanently sterilized will not undergo pregnancy testing.

6.5.4.3. 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 (see Table 3). Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory, all assessments in Table 6 will be performed one time, as well as hematology, serum chemistry, LFT, and coagulation assessments per Table 3, and other assessments or evaluations per Investigator discretion, as appropriate.

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

Table 6: Hepatic Assessments in Patients Who Experience Elevated Transaminases

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

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

Note:

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

6.5.5. Adverse Events

6.5.5.1. Definitions

Adverse Event

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

Serious Adverse Event

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

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

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- ALT or AST >3× ULN
- Severe or serious ISRs; ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or ISRs 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 6.5.5.2 and Section 6.5.5.3, 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 AE.

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

Adverse event 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.

6.5.5.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in the patient's health since the last visit. The patient 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, 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 EOS. Non-serious AEs will be followed until the EOS. Events occurring after signing of the ICF and before study drug administration will be captured as medical history (see Section 6.1), while AEs that occur after study drug administration, and baseline events that worsen after study drug administration, must be recorded as AEs.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the EOS. Serious AEs 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 the eCRF and, as applicable, the SAE form.

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), the supplemental AEs of Clinical Interest eCRF should be completed. Additional clinical and laboratory information may be collected. Refer to eCRF completion guidelines for details on reporting events in the supplemental AEs of Clinical Interest eCRF.

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

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

For AEs that are considered AEs of clinical interest (Section 6.5.5.1), 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 eCRF 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).

6.5.5.4. 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 6.5.5.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious

- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF and, as applicable, the SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the eCRF and, as applicable, the SAE form. Serious AEs 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.

6.5.5.5. 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.

6.5.5.6. 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.

6.5.5.7. Pregnancy Reporting

If a female patient becomes pregnant during the study through 6 months following the last dose of study drug, 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 6 months 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 6.5.5.4.

The reporting of any pregnancy outcome for a female partner of a male patient participating in this study that results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly should be reported to the Investigator, who will then report this to the Sponsor or designee. The pregnancy outcome is to be recorded on the pregnancy reporting form.

6.5.5.8. Reporting of Overdose and Other Special Situations

An overdose is defined as any dose of study drug administered to the participant that is ≥2-fold the assigned dose during a single administration.

The Sponsor does not recommend specific treatment for an overdose.

In an event of an overdose or other special situations (eg, medication error, abuse, misuse, CPC associated with an AE), the Investigator should:

- Contact the Medical Monitor within 24 hours
- Submit the special situations reporting form within 24 hours using the contact information in the Pharmacy Manual
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the amount of study drug given

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication will be considered AEs/SAEs. Overdose per se will not be categorized as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported as an SAE regardless of sequelae.

Full details of overdose and other special situations reporting instructions will be outlined in the Pharmacy Manual.

6.6. Biomarkers, Exploratory 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 recurrent calcium oxalate kidney stone disease, as well as their responses to treatment.

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

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

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

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

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

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

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

6.7. Quality of Life Outcomes

6.7.1. Pain Assessment

Patients will be asked to assess their "worst daily pain" (0=no pain at all; 10=pain as bad as you can imagine) from Question 3 of the Brief Pain Inventory - Short Form. This will be administered at screening, on Day 1, and daily while experiencing stone-related pain until the conclusion of the associated stone event.

6.7.2. Wisconsin Stone Quality of Life Questionnaire

The Wisconsin Stone Quality of Life Questionnaire (WISQOL) will be administered on Day 1 and upon conclusion of each clinical kidney stone event (as defined in Section 6.2.2.1) and will assess the degree of kidney stone impacts in terms of:

- Fatigue
- Sleep
- Social function
- Daily activities
- Physical / psychosocial symptoms

6.8. Healthcare Utilization

To complement medical records, information regarding health resource use related to kidney stone events will be collected as specified in the Schedule of Assessments (Table 1), including emergency room visits, unscheduled office visits, hospitalizations, and procedures for kidney stone management.

7. STATISTICS

A Statistical Analysis Plan (SAP) will be finalized before database lock and study unblinding for the primary analysis. The plan will detail the implementation of the statistical analyses in accordance with the principal features stated in the protocol.

7.1. Determination of Sample Size

The planned enrollment for this study is 120 patients.

The study is powered to detect a difference in urinary oxalate excretion between each lumasiran group and the placebo group. Assuming a standard deviation of 45% in the percent change from baseline in 24-hour urinary oxalate levels at Month 6, a sample size of 40 patients per group will enable a power of at least 80% in detecting a treatment difference of 30% between the treatment groups at a 2-sided significance level of 0.05. Table 7 shows the statistical power under various assumptions for a sample size of 40 per group.

Table 7: Sample Size Power Calculations

Assumed standard deviation (SD)	Assumed difference (lumasiran – placebo)	Power
25%	20%	94%
	30%	99%
30%	20%	84%
	30%	99%
45%	20%	50%
	30%	84%

Abbreviations: SD=standard deviation

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 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 at least 1 dose of study drug. Patients in the FAS will be analyzed according to the randomized treatment arm.
- **Safety Analysis Set:** All randomized patients who received at least 1 dose of study drug. Patients in the Safety Analysis Set will be analyzed according to the treatment actually received.

- **PK Analysis Set:** All patients who received at least 1 full dose of study drug and have at least one postdose blood sample for PK parameters and have evaluable PK data.

The primary population used to evaluate efficacy will be the FAS. Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses.

7.2.2. Examination of Subgroups

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

7.2.3. Handling of Missing Data

Handling of missing data will be described in the SAP.

7.2.4. Baseline Evaluations

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

7.2.5. Efficacy Analyses

The hypothesis testing for the primary endpoint will be tested comparing each lumasiran group to the placebo group in the FAS with a 2-sided significance level of 0.05.

The primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM) approach. The outcome variable is percent change from baseline in urinary oxalate to Month 6 (average across Months 4 through 6). The model includes baseline value and the stratification of number of historical kidney stone events (>1 versus ≤1 event in the 12 months prior to screening) as covariates, and fixed effect terms including treatment arm, visit and visit and treatment arm interaction. The estimate of treatment difference for the average percent change from baseline of 24-hour urinary oxalate excretion across Months 4 through 6 will be calculated via a linear contrast of the corresponding coefficients from the MMRM model.

Additionally, the percent change from baseline in 24-hour urinary oxalate excretion at Month 9 and Month 15 will be summarized and compared between lumasiran and placebo treatment groups.

Baseline, Month 9, and Month 15 urinary oxalate values and urinary calcium oxalate supersaturation values are planned to be collected in either duplicate or triplicate (baseline) and duplicate (Months 9 and 15), and the calculated median of valid collections during each time period (visit) will be used in the analysis.

Analysis of secondary endpoints and exploratory endpoints will be specified in the SAP. No multiplicity adjustment is planned.

7.2.6. Pharmacodynamic Analysis

The change in plasma oxalate and plasma and urinary glycolate will be summarized over time for all patients in the FAS.

7.2.7. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods.

Pharmacokinetic parameters to be calculated include but will not be limited to maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}). Other parameters may be calculated, if deemed necessary.

7.2.8. Safety Analyses

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

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

Descriptive statistics, summarizing the observed values and changes from baseline over time, will be provided for clinical laboratory parameters and vital signs. Laboratory shift tables from baseline grade (or category) to worst post-baseline grade (or category) will be presented for laboratory parameters that are graded or categorized. Abnormal physical exam findings will be presented in listings.

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

7.2.9. Immunogenicity Analyses

The frequency and percentage of patients with confirmed positive ADA assay at any time during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will be summarized.

7.2.10. Other Analyses

Other exploratory analyses will be described in the SAP.

7.2.11. Interim Analysis

No formal interim analysis is planned. The primary analysis will be conducted for the primary and secondary endpoints through Month 6 after the last patient has completed the Month 6 visit, the database is locked, and data are unblinded.

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 ICF (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 is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator will inform the patient if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. Communication of this information should be documented. If circumstances warrant an updated informed consent during the study, and patients are required to re-consent, this may be collected remotely where local regulations allow.

The patient's signed and dated informed consent (in paper or electronic format per local regulations and institutional standards) must be obtained before conducting any study tests or procedures that are not part of routine care.

The Investigator must maintain the original, signed ICF. All patients will be given a copy of the signed and dated ICF.

8.1.2. Ethical Review

The study protocol, including the ICF, 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 or IEC approval of the protocol, and all materials approved by the IRB or IEC for this study including the patient consent 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 6.5.5. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

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

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

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

8.1.3. Serious Breach of Protocol

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

8.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation (including personal data) relating to the study should be retained for 2 years after the last approval in an ICH territory or as required by local laws and regulations, 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 to be submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number added to the document, before sending to the Sponsor. 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 EOS is defined as the last patient last visit.

8.1.6. Termination of the Clinical Study or Site Closure

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

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

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

8.2. Data Quality Control and Quality Assurance

8.2.1. Data Handling

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

8.2.2. Study Monitoring

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

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

Where local regulations allow, the Monitor may request remote access to source documents and systems. Should this take place, it will be done in a manner that protects the confidentiality of the data.

8.2.3. Audits and Inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor and designee immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

8.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed publication (eg, manuscript, abstracts, oral/slide presentations, book chapters) based on this study, must be provided and confirmed received at the Sponsor at least 30 days before its submission. The Clinical Trial Agreement will detail the procedures for 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. Formula for Estimated Glomerular Filtration Rate Calculation

CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

- Conventional units
  - eGFR (mL/min/1.73m^2) = 175 × (SCr [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)

Abbreviations: eGFR= Estimated glomerular filtration rate; SCr=serum creatinine; SI=International System of Units