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**

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STATISTICAL ANALYSIS PLAN
ALN-GO1-008

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:	2
Protocol Date:	Original Protocol: 24 June 2021
SAP Date:	Original SAP: 31 March 2022
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel test
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
FA	Final analysis
FAS	Full Analysis Set
HLT	High Level Term
IRT	Interactive Response Technology
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
Q1	First quartile

Abbreviation	Definition
Q3	Third quartile
QOL	Quality of life
RBP	Randomization and blinding plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SMQ	Standardized MedDRA queries
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

1. INTRODUCTION

This statistical analysis plan (SAP) details comprehensive specifications of the statistical analyses of efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data in support of the clinical study report for Study ALN-GO1-008. Table, figure, and listing (TFL) mocked shells and specifications are contained in a separate document.

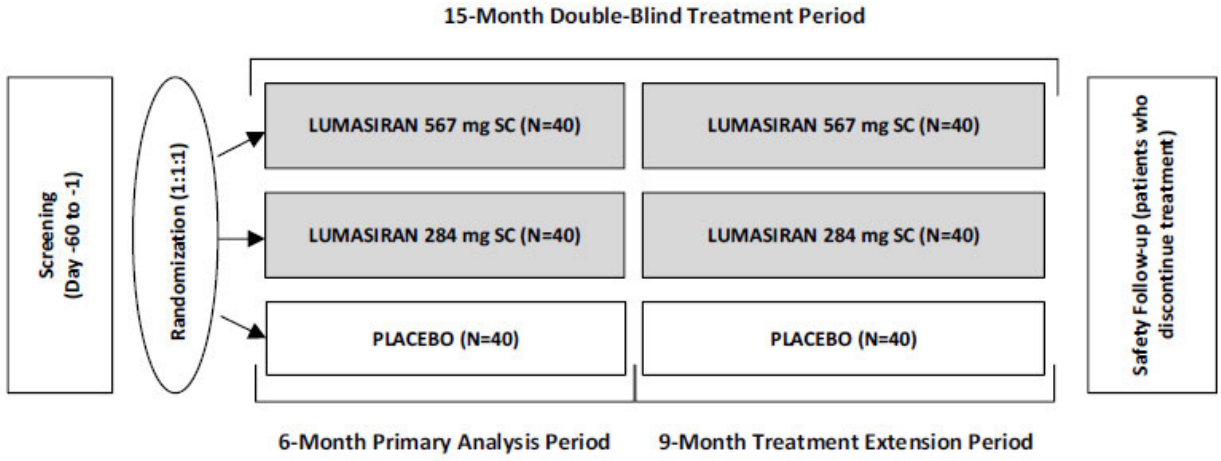
2. STUDY DESIGN

2.1. Synopsis of Study Design

The ALN-GO1-008 study is a multi-center, multinational, Phase 2 study designed 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. The study consists of a screening period of up to 2 months, a 1:1:1 randomized, placebo-controlled, double-blind (DB) treatment period of 15 months (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period), and a safety follow-up for patients who discontinue treatment early.

The study design schema is presented in Figure 1.

Figure 1: Study Design



Abbreviations: SC=subcutaneous(ly)

2.2. Objectives and Endpoints

2.2.1. Objectives

2.2.1.1. Primary Objective

- To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion

2.2.1.2. Secondary Objectives

- To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran
- To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation

2.2.1.3. Exploratory Objectives

- To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion
- To evaluate the effect of lumasiran on the occurrence of kidney stones
- To evaluate additional PD parameters of plasma oxalate, plasma glycolate, and urinary glycolate
- To characterize PK of lumasiran
- To assess for antidrug antibodies (ADA) against lumasiran
- To evaluate the effect of lumasiran on spot urinary oxalate:creatinine ratios
- To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time
- To evaluate the effect of lumasiran on maintaining 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
- To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)
- To evaluate the effect of lumasiran on patient healthcare resource utilization
- To assess the impact of kidney stone events on patient-reported pain and quality of life (QoL)

2.2.1.4. Safety Objective

- To evaluate the safety and tolerability of lumasiran

2.2.2. Endpoints

2.2.2.1. Primary Endpoint

- Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)

2.2.2.2. Secondary Endpoints

- Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
- Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)

2.2.2.3. Exploratory Endpoints

- Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
- Incidence rate of clinical and radiographic kidney stone events
- Time to first kidney stone event
- Change from baseline in plasma oxalate
- Change from baseline in plasma glycolate
- Change from baseline in urinary glycolate
- Plasma PK of lumasiran
- ADA frequency and titer
- Change from baseline in spot urinary oxalate:creatinine ratios
- Percentage of patients with 24-hour urinary oxalate ≤ULN over time
- Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
- Change from baseline in 24-hour urinary oxalate excretion after Month 6
- Change from baseline in eGFR
- Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
- Patient-reported severity and symptomatic and functional impact of kidney stone events

2.2.2.4. Safety Endpoint

- Frequency of AEs

2.3. Study Procedures

The Schedule of Assessments from the protocol is included as Section 7.1.

2.4. Randomization Methodology

Patients will be randomized 1:1:1 to receive lumasiran 284 mg, lumasiran 567 mg, or placebo in a DB manner. 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, 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
  - 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.

2.5. Blinding

The randomization schedule is maintained by the interactive response technology (IRT) vendor. Alnylam is unblinded throughout the entire study. However, during the 15-month DB treatment period, investigators, site personnel, patients, and selected vendor personnel as outlined in the Randomization and Blinding Plan (RBP), will remain blinded to treatment assignment and any clinical laboratory results that could potentially unblind them, including PK data, ADA, and PD data (post-baseline results for 24-hour urinary oxalate, spot urinary oxalate:creatine, plasma oxalate, plasma and urinary glycolate, urinary calcium oxalate supersaturation), until study unblinding which will occur after all patients have completed Month 15 visits.

Unblinding is only to occur in the case of patient emergencies, or when necessary from a regulatory reporting perspective (eg, Suspected Unexpected Serious Adverse Reaction [SUSAR]), or after all patients have completed the 15-month DB treatment period and the unblinding authorization has been executed.

Details about the specifics of the blinding aspects for the study are outlined in the RBP.

2.6. 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 1 shows the statistical power under various assumptions for a sample size of 40 per group.

Table 1: 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

No multiplicity adjustment is considered in the sample size calculation.

3. ANALYSIS POPULATIONS

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 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 1 post-dose blood sample for PK parameters and have evaluable PK data.
- 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 (LLOQ). The LLOQ of the plasma oxalate assay is 5.55 µmol/L. Because it is not possible to quantify plasma oxalate levels below LLOQ using the assay, patients with baseline plasma oxalate levels near the LLOQ (ie <1.5*LLOQ) are excluded from the analysis to ensure that meaningful reductions in plasma oxalate can be evaluated for the study population.

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. Both the FAS and Safety Analysis Set will be used to summarize demographic and baseline disease characteristics. The Safety Analysis Set will be used for medical history, prior and concomitant medications, and protocol deviations. The Plasma Oxalate Analysis Set will be used to evaluate the endpoint for the change from baseline in plasma oxalate.

4. GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses will be conducted using SAS software Version 9.4 or newer or R version 3.6 or newer.

4.1. General Considerations

Categorical variables will be summarized using counts and percentages. The percentage will not be presented for a count of zero.

Continuous variables will be summarized using the following descriptive summary statistics: number of patients (n), mean, standard deviation (SD), standard error of the mean (SEM), median, first quartile (Q1), third quartile (Q3), minimum, and maximum. The same level of precision collected in the database will be displayed for the minimum and maximum, plus one additional decimal for the mean and median, plus 2 additional decimals for SD and SEM.

For 24-hour urinary oxalate, urinary calcium oxalate supersaturation, and 24-hour urinary glycolate:creatinine ratios, the median of valid collections will be used as the value at any visit where multiple collections are done because of the variability of these parameters. For other PD parameters, the mean of all assessments will be used if multiple collections are done at a given visit. For safety laboratory parameters, assessments collected and recorded as lower than the LLOQ will be replaced by the LLOQ. Any assessment collected and recorded as greater than the upper limit of quantification (ULOQ) will be replaced by the ULOQ. The day of the first dose of study drug administered is defined as Day 1. The Study Day of a time point of interest is calculated as follows.

If on or after Day 1, Study Day = date of interest – date of the first dose of study drug + 1

If prior to Day 1, Study Day = date of interest – date of the first dose of study drug

There is no Day 0. For example, the day before the first study drug dose is defined as Day -1.

All descriptive summaries will be presented by treatment arm (lumasiran 284 mg, lumasiran 567 mg, placebo) and overall, where applicable. In addition to presentation by treatment arm, a pool of lumasiran 284 mg and 567 mg will also be presented as all lumasiran treatment for the safety analysis.

4.2. Multiple Comparisons/Multiplicity Procedure

No multiplicity adjustment is planned.

4.3. Handling of Missing Data

No explicit imputation will be done for missing values for the analyses of the primary, secondary, or exploratory endpoints. For all analyses using mixed-effect model for repeated measures (MMRM), the model makes use of all available data, including patients with partial data (i.e., with missing data), to estimate the mean treatment effect without employing formal imputation.

4.4. Baseline Definitions

Baselines for efficacy parameters are defined as follows:

- For 24-hour urinary oxalate, urinary calcium oxalate supersaturation, and 24-hour urinary glycolate:creatinine ratios, baseline will be defined using the median value from all valid 24-hour urine collections obtained prior to the date of the first dose of study drug.
- For other PD parameters, baseline will be defined as the mean of all measurements collected prior to the first dose of study drug.

For laboratory parameters and vital signs, baseline will be defined as the last non-missing value available (scheduled and unscheduled) prior to the date and time of the first dose of lumasiran.

4.5. Randomization Stratification Factors

The 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) will be used as stratification factors. These stratification factors are recorded in both the IRT and the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database (EDC). In the presence of stratification errors, the stratification used in analysis may not match that in the IRT. A comparison of the number and percentage of patients in each randomization stratification factor in IRT versus the clinical database will be summarized by randomized treatment arm and overall.

4.6. Planned Analyses

The primary analysis will be performed after all randomized patients have completed the Month 6 visit or discontinued from the study. For the primary analysis, as this study will be ongoing with some patients in the 9-Month Treatment Extension Period, the study database will be locked with all data up to a prespecified cutoff date quality controlled, ie, data in the EDC system will be cleaned and frozen and external laboratory data will be cleaned and quality controlled (and quality assured, where appropriate).

The primary analysis will include data on or prior to this prespecified cutoff date. For the efficacy summaries, all data up to and including the Month 6 visit will be presented. For assessments with start and end dates (eg, AEs, medications), the start date will be compared with the pre-specified cutoff date. Data records with start dates after the specified data cutoff date will be excluded.

The final analysis will be conducted after all patients have completed the Month 15 visit or discontinued from the study. The database will undergo a final lock.

Additional details regarding the database lock process are located in the study Data Management Plan.

4.7. Visit Windows

For PD and safety parameters, no window rules will be implemented, and the reported eCRF visits will be used for analysis.

The following general conventions for unscheduled assessments will apply unless otherwise specified:

- If by-visit summaries are based on CRF Visit, only scheduled assessments will be included in by-visit summaries. Unscheduled assessments will not be included.
- Unscheduled assessments will be used in the calculation of baseline values and for shift from baseline to worst post-baseline tables. They will also be included in by-patient listings and spaghetti plots.

5. STATISTICAL ANALYSES FOR THE DOUBLE-BLIND PERIOD

5.1. Patient Disposition

The number and percentage of patients in the following categories will be summarized by treatment arm and overall, for the FAS and Safety Analysis Set:

- Randomized
- Treated
- Completed the Month 6 visit
- Completed treatment
- Completed the study
- Discontinued treatment and primary reason for discontinuation of treatment
- Withdrew from study and primary reason for withdrawal from study

A patient is defined as having completed the Month 6 visit if the patient has any of the assessments required for the Month 6 visit.

The number and percentage of patients who met criteria for the FAS, Safety Analysis Set, and PK Analysis Set will be summarized by all randomized patients.

The number and percent of patients enrolled by country and site will be summarized by randomized arm and overall.

Screen failures and the reason for screen failure will be summarized by all screened patients.

A data listing for treatment/study completion information along with the primary reasons for treatment discontinuation and/or study withdrawal will be generated.

5.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment arm and overall using the FAS and Safety Analysis Set, and also presented in listings.

Demographic characteristics including age at screening (years), height (cm), weight (kg), and body mass index (BMI [kg/m^2]) will be summarized using descriptive statistics. Age group (18 to <65, ≥65), sex, race, ethnicity, and region (US, Europe) will be summarized by presenting the frequencies and percentages of patients in each category.

Baseline disease characteristics including 24-hour urinary oxalate excretion (mg/24hr), urinary calcium oxalate supersaturation (DG), plasma oxalate (µmol/L), plasma glycolate (µmol/L), 24-

hour urinary glycolate:creatinine ratios (mmol/mmol), spot urinary oxalate:creatinine ratios (mmol/mmol), and eGFR (mL/min/1.73m^2) will be summarized by descriptive statistics. Heterozygosity for any *AGXT* mutation (Yes/No) will be summarized by the number and percentage of patients in each category.

A tabulation of historical kidney stone events that occurred within 5 years prior to screening and within 12 months prior to screening will be presented. The number of kidney stone events will be summarized using descriptive statistics. Additional characteristics will be summarized by presenting the numbers and percentages of patients in each category:

- Patients with at least one kidney stone event (visible passage of kidney stones, a procedural intervention for removal of an asymptomatic or symptomatic stone, a new or enlarged kidney stone on CT imaging)
- Patients with at least one kidney stone event related hospitalizations, emergency room visits, urgent care, or urgent/unscheduled office visits
- Patients with a stone composition >50% calcium oxalate from the 2 most recently analyzed kidney stones (Yes/No)
- Patients for whom only 1 kidney stone was available for composition analysis

5.3. Medical History

Medical or surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or newer. Unique patients who report medical history events will be summarized and listed for the Safety Analysis Set by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT).

5.4. Protocol Deviations

Protocol deviations will be classified by medical review prior to the 6-month primary analysis and prior to the FA database lock. Major protocol deviations will be identified in the protocol deviation file. A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being (ICH E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry, 2013).

The Sponsor or designee will be responsible for producing the protocol deviation file. This file will include a description of each protocol deviation and whether each deviation is classified as major. The file will be reviewed and finalized prior to the 6-month primary analysis database lock and prior to the FA database lock.

All protocol deviations and major protocol deviations will be summarized and listed for the Safety Analysis Set.

5.5. Study Drug Exposure and Compliance

The following variables will be summarized by descriptive statistics and/or frequency tabulation for the Safety Analysis Set:

- Duration of study drug exposure (months), defined as: (date of last exposure – date of first dose +1)/30.44. Date of last exposure is the earliest date of the following:
  - date of last dose + 168 days (eg, the length of the longest dosing interval)
  - date of end of study
  - date of data cutoff for the analysis
- Cumulative study drug exposure time (patient-years)
- Number of patients on study drug for ≥1 day, ≥3 months, ≥6 months
- Number of doses received as continuous and categorical variables (1, 2, or 3)
- Cumulative number of doses received
- Number of missed doses (0, 1, 2, or 3) as a categorical variable
- Total study drug exposure (mg) as a continuous variable
- Total volume administered (mL)

5.6. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version B3 WHO Drug Global - Sep 2018 or newer. Unique patients who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class (or level 2 if not available) and PT. Summaries and listings for the Safety Analysis Set will be provided for prior and concomitant medications separately.

Prior medications are defined as medications with start date and stop date prior to the first dose of study drug. Concomitant medications are medications, other than the study drug, administered on or after the first dose date of study drug, as well as medications that started prior to the first dose of study drug and are ongoing after the first dose of study drug. If medication start date is on or after the date of first dose of study drug, the medication will be summarized as a concomitant medication even if the medication end date is missing. If the end date of a medication is missing or incomplete such that it cannot be determined whether it is after the first dose of study drug, it will be counted as a concomitant medication.

For missing or partial dates for medications, the imputation of start and end dates is described in Section 7.3.

5.7. Efficacy Analyses

5.7.1. Primary Endpoint(s)

5.7.1.1. Definition of Estimand

For the primary objective of evaluating the efficacy of the study drug lumasiran compared with placebo on the percent change in urinary oxalate excretion, the primary estimand is defined as follows:

- **Target population**: Patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels.
- **Treatment condition**: Lumasiran 284 mg, lumasiran 567 mg, or placebo administered by SC injection at Day 1, Month 3, and Month 9
- **Endpoint**: the percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
- **Population-level summary**: the least square (LS) mean difference in percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6) between each lumasiran dose group and the placebo arm.
- **Strategies for intercurrent events (ICE)**:

Table 2: Intercurrent Event Strategies for the Primary Analysis of Primary Endpoint

Intercurrent Event	Strategy with Rationale
Selected medication of vitamin C equivalence[1]	Hypothetical strategy: 24-hour urinary oxalate collection will be excluded from the analysis if dose of vitamin C equivalent to ≥500 mg in a single day is taken at any point within 4 days prior to the start of or during the urine collection. Rationale: vitamin C can be converted to oxalate, confounding urinary oxalate measurement.

[1] To identify vitamin C equivalence, two Alnylam physicians will each conduct an independent review of the concomitant medications to identify medications containing vitamin C. If there are any discrepancies, a meeting will be held to reach a consensus on each discrepancy. Once the medications are identified, the Alnylam DSS team will programmatically identify the total dose of vitamin C taken in a single day.

5.7.1.2. Primary Analysis

The hypothesis testing for the primary endpoint will be tested comparing each lumasiran group to the placebo group during the 6-month primary analysis period in the FAS with a 2-sided significance level of 0.05.

The primary endpoint will be analyzed using an MMRM approach using the ICE strategy described in Table 2. The outcome variable is percent change from baseline in 24-hour urinary oxalate to Month 6. The model includes baseline 24-hour urinary oxalate (as defined in Section 4.4) 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 (lumasiran 567 mg or lumasiran 284 mg vs placebo), visit (Months 3, 4, 5, 6) and treatment-by-visit interaction. The primary treatment effect estimate from this model will represent the average percent change from baseline in 24-hour urinary oxalate across months 4 through 6, which is calculated via a linear contrast of the corresponding coefficients from the MMRM model. An unstructured covariance structure matrix will be used to model within-patient error. If the fit of the unstructured covariance structure matrix fails to converge, then the following covariance structure will be assessed in this order: autoregressive (1), compound symmetry, Toeplitz. The Satterthwaite approximation will be used to estimate the denominator degrees of freedom.

The LS mean, standard error of the mean (SEM), 95% confidence interval (CI), and p-value will be generated for each treatment arm and the treatment difference between each lumasiran dose

and placebo from Months 4 through 6. In addition, the LS means, SEM, and 95% CI will also be generated for each visit (Months 3, 4, 5, 6) by treatment arm.

5.7.1.3. Sensitivity Analyses

A sensitivity analysis will be conducted including all data without censoring assessments after the initiation of select vitamin C equivalent medications.

5.7.1.4. Other Analyses

Descriptive statistics will also be generated for the actual values, change from baseline, and percent change from baseline at each scheduled visit by treatment arm. LS Mean (+/- SEM) figures of percent reduction by treatment arm will be plotted as well as individual spaghetti plots. Listings will also be generated.

The exploratory endpoint of absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6) will be analyzed using the MMRM model specified for the primary endpoint.

5.7.2. Secondary Endpoints

The percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the 2 stratification factors (Section 4.5). The odds ratio with the corresponding 95% CI and associated p-value will be presented. In addition, the differences in proportion of responders and corresponding 95% CI using the Newcombe method based on the Wilson score will also be presented. In addition, a tabulation and a bar chart showing the proportion of patients with a ≥20% reduction in 24-hour urinary oxalate from baseline to each visit and on average across Months 4 through 6 will be presented.

For the analysis of urinary calcium oxalate, selected medication could potentially impact the endpoint, therefore the assessments will be excluded from analysis if patients start, stop, or change any of the following medications within a specified time frame of the data collection:

- Vitamin C equivalent to ≥500 mg in a single day is taken at any point within 4 days prior to the start of or during the urine collection (see Table 2)
- The patient is on a new daily dose (relative to screening) of hydrochlorothiazide, allopurinol, topiramate, acetazolamide or furosemide at any point within 4 days prior to the start of or during the collection
- Urine alkalinization agents (potassium citrate, potassium citrate-citric acid, sodium citrate-citric acid, sodium citrate-potassium citrate-citric acid, sodium bicarbonate, potassium bicarbonate, or potassium bicarbonate-potassium citrate) started, stopped, or changed at any point within 2 days prior to the start of or during the collection (relative to screening)

Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6) will be analyzed using the same MMRM approach as for the primary endpoint. Descriptive statistics will also be generated for the actual values, change from baseline, and percent change from baseline at each scheduled visit by treatment arm. LS Mean (+/- SEM)

figures of percent reduction by treatment arm will be plotted as well as individual spaghetti plots. Listings will also be generated.

A sensitivity analysis of the percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6) will also be analyzed using the same approach as the main analysis above including all data without excluding assessments that could potentially be impacted by selected mediations.

5.7.3. Exploratory Endpoints

Apart from the 24-hr urinary oxalate, all other exploratory endpoints will be by treatment arm (lumasiran 567 mg, lumasiran 284 mg, placebo) during the 6-month primary analysis period using the FAS. These endpoints will also be summarized for the 15-month DB period by treatment arm using the FAS. The change from baseline in 24-hr urinary oxalate will be summarized after Month 6. Listings will also be generated for each exploratory endpoint below.

5.7.3.1. Kidney Stone Events

CT scans for radiographic kidney stone events are read in pairs blinded to visit date (baseline and Month 15). All kidney stone-related analyses in this section will be done with all data collected.

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.

A radiographic kidney stone event is defined as a kidney stone that is increased in size by ≥2 mm in at least one dimension or a new stone (≥1 mm in size) observed on CT at Month 15 relative to baseline.

Time to first kidney stone event

Time to first event is defined as date of the first study drug to the first date of a kidney stone event. Censoring applies to patients who do not have a kidney stone event during the study. The follow-up time of these patients will be censored at the lost to follow-up date, study discontinuation, data cut-off date, or end of study, whichever occurs first.

Time to the first kidney stone event will be analyzed for a combination of both clinical and radiographic kidney stone events and for clinical kidney stone events separately for both the 6-month primary analysis period and the 15-month DB period (FA). All available data at the time of each database lock will be used. Kaplan-Meier estimator will be used to estimate the distribution of time to first kidney stone event in each treatment group. A log-rank test will be used to evaluate the treatment differences between each dose and the placebo. In addition, Cox proportional hazard regression will be performed to estimate the hazard ratio along with the 95% CI and p-value for each dose compared to the placebo. The model includes treatment, number of historical kidney stone events (>1 versus ≤1) in the 12 months prior to screening.

Incidence rate of clinical and radiological kidney stone events

The incidence rate of kidney stone events will be analyzed for a combination of both clinical and radiographic kidney stone events and for clinical kidney stone events separately for both the 6-month primary analysis period and the 15-month DB period (FA).

The incidence rate will be calculated as the total number of kidney stone events divided by total person-years at risk during the respective period (ie, 6-month primary analysis period and 15-month DB period). Years at risk is defined as (time from first lumasiran dose until 168 days after the last dose of lumasiran, lost to follow-up date, study discontinuation, data cut-off date, or end of study, whichever occurs first)/365.25.

The endpoint will be analyzed using a negative binomial regression model that include fixed effects of the treatment arm and the number of historical kidney stone events (>1 versus ≤1) in the 12 months prior to screening. The logarithm of the follow-up time of each patient will be included in the model as an offset variable. The p value and the ratio of mean kidney stone event rate between two treatment arms with the corresponding 95% CI will be estimated.

The total number of patients with at least one kidney stone event, total number of kidney stone events, total number of person-years will be presented. Descriptive statistics for the median and interquartile range of the kidney stone event rate will also be presented by treatment arm.

Other radiographic assessments

Change from baseline in radiographic assessments of kidney stones (eg stone volume) will be summarized descriptively.

5.7.3.2. Pharmacodynamics

The PD exploratory endpoints are described in Section 5.8.

5.7.3.3. Change from Baseline in eGFR

Descriptive statistics of eGFR along with mean (+/-SEM) figures and individual spaghetti plots will be presented for the actual values, change from baseline, and percent change from baseline for each treatment arm by visit.

5.7.3.4. Healthcare Utilization and Quality of Life

Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures

Healthcare utilization associated with a kidney stone event will be descriptively summarized for the number of visit type (hospitalization, emergency room, urgent care center, unscheduled office visit, other) per patient, cumulative length of hospital stay (days), and cumulative length of stay in the ICU. The number of, and percent of, patients with different type of visits (hospitalization, emergency room, urgent care center, unscheduled office visit, other) will also be presented.

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

Quality of life (QoL) outcomes will be summarized using a two-sample t-test for the difference between the mean scores of each lumasiran dose to the placebo. The analyses will be performed

using the worst scores post-baseline as reported by the patients and also using the scores from the most severe clinical kidney stone event as graded by the investigators (Refer to protocol Section 6.5.5.1 for definition of clinical kidney stone grade).

The QoL will also be summarized by treatment group for the actual values, change from baseline (Day 1), and percent change from baseline to the first clinical kidney stone event, to the most severe clinical kidney stone event as graded by the investigators, and to worst scores post-baseline as reported by the patients. Baseline for the Brief Pain Inventory-Short Form (BPI-Short Form) is defined as the mean score during Screening and Day 1 visits. This summary will be done excluding patients who have a kidney stone event during Screening/Day 1 as a sensitivity analysis.

For the QoL analyses, if a patient has multiple clinical kidney stones with the same grade, the first severe clinical kidney stone event will be used for the analysis.

- [redacted]
- [redacted]

5.7.4. Evaluation of Subgroups

Subgroup analyses will be conducted to assess the consistency of treatment effect within the various subgroups defined by the following baseline characteristics:

- Age (18 to <65, ≥65)
- Sex (Male, Female)
- Race (White, Black, All others)
- BMI (kg/m^2) (<30; ≥30)
- *AGXT* heterozygous (Yes/No)
- 24-hr urinary oxalate (≤1.25 ULN, >1.25 ULN)
- Historical kidney stone events in the 12 months prior to screening (≤1, >1)

- Calcium oxalate stone composition (≤75%, >75%)
- History of diabetes (Yes, No)

Subgroup analyses will be performed for the primary endpoint of percent change in 24-hour urinary oxalate to Month 6 using the FAS population. A forest plot will be generated to illustrate the estimated treatment effect along with the associated 95% CI. If the number of patients in a subgroup for either arm is less than 10 patients, then only descriptive statistics will be generated.

Other subgroups may be examined, if deemed appropriate. The subgroup analyses may also be performed for other efficacy endpoints.

5.8. Pharmacodynamic Analyses

The PD parameters include plasma oxalate, plasma glycolate, 24-hour urinary glycolate:creatinine ratios, and spot urinary oxalate:creatinine ratios. Summary tables, mean (+/- SEM) figures, and individual spaghetti plots will be provided for observed values, absolute changes, and percentage changes from baseline for each scheduled time point by treatment group. FAS is used for all PD parameters except for plasma oxalate where a separate analysis population, Plasma Oxalate Analysis Set is used.

The number and percent of patients with 24-hour urinary oxalate ≤ULN (40 mg) and the number and percent of patients having a 25% reduction in urinary calcium oxalate supersaturation will be presented over time.

5.9. Pharmacokinetic Analyses

Plasma lumasiran concentrations by visit will be summarized descriptively for the PK Analysis Set.

5.10. Anti-Drug Antibodies

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any post-baseline visit during the 6-month primary analysis period, as well as treatment-emergent ADA during the 6-month primary analysis period, will be summarized and listed for the Safety Analysis Set. The same summary and listing will also be done for the Month-15 DB period.

Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, as defined below:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

5.11. Safety Analyses

Safety analyses will compare both doses of lumasiran combined and separately versus placebo using the Safety Analysis Set.

5.11.1. Adverse Events

Adverse events (AEs) will be classified by the MedDRA coding system (version 24.1) and displayed in tables and data listings using SOC and PT.

Treatment-emergent AEs (TEAEs) will be summarized, where TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and through 168 days after the last dose or any study drug-related AE. Because any worsening AE is reported as a new AE with higher severity, programmatical comparison of severity is not needed for the classification of TEAE. For missing or partial dates for AEs, the imputation of start and end date can be found in Section 7.3. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first dose of study drug. All TEAEs hereafter will be referred to as AEs in this document.

AEs will be summarized by the numbers and percentages of patients reporting a given AE. An overall table of TEAEs will include, but not limited to:

- At least 1 AE
- At least 1 drug related AE
- At least 1 severe AE
- At least 1 drug related severe AE
- At least 1 Serious Adverse Event (SAE)
- At least 1 drug related SAE
- At least 1 AE leading to treatment discontinuation
- At least 1 AE leading to drug interruption
- At least 1 drug related AE leading to treatment discontinuation
- At least 1 AE leading to study withdrawal
- At least 1 drug related AE leading to study withdrawal
- Death (based on SAE CRFs)

Tabulations by SOC and PT will be produced for the following:

- AEs,
- Treatment-related AEs,
- AEs by maximum severity,
- Treatment-related AEs by maximum severity,
- Severe AEs,
- Treatment-emergent SAEs,
- AEs leading to treatment discontinuation.

Tabulations by PT in decreasing order in frequency within each treatment arm will be produced for the following:

- AEs
- Treatment-related AEs
- SAEs

AEs and AEs related to treatment will also be summarized by severity. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence. An AE with missing severity will be assumed to be severe. An AE with missing study drug relatedness will be assumed to be related.

Listings of all deaths, SAEs, and AEs leading to treatment discontinuation will be provided.

Selected AE tabulations will include number of AEs and event rates per patient-year. In these summaries, multiple occurrences of the same AE in a patient will be counted multiple times for that patient.

AE summary tables (by SOC and PT) will be separately generated for each of the subgroups below:

- Sex (Male, Female)
- Race (White, Black, All other)
- Region (US, Europe)

AEs of Clinical Interest

The following AECI will be summarized by SOC and PT:

- Severe or serious injection site reactions (ISRs): AEs mapping to the HLT "Injection Site Reactions" using MedDRA dictionary.

  A tabulation will also be generated to display the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose in summary), total number of doses with ISRs, and the signs and symptoms reported due to ISRs. If there are multiple ISRs that occur in between 2 consecutive injections, then these events will be considered as 1 ISR and considered related to the earlier injection.
- ALT or AST >3xULN: AEs mapping to certain standardized MedDRA queries (SMQs) will be summarized by SOC and PT.

All AEs will be presented in patient data listings. AEs mapping to the SMQs as described above will also be listed.

5.11.2. Laboratory Data

Clinical laboratory values will be expressed in SI units. Missing laboratory data will not be imputed.

For each continuous clinical laboratory parameter (hematology, serum chemistry, and liver function tests), descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit. These by-visit tables will use central laboratory data only. eGFR will not be reported in this section, as this is summarized in the efficacy section (Section 5.7.3.3). For any local collections of LFTs and others, these will be included in a separate data listing.

Select clinical laboratory parameters may be graded according to the National Cancer Institute CTCAE Version 5.0 or above. Shift summary from baseline CTCAE grade to maximum (worst) post-baseline grade will be presented for all graded parameters with directionality specified (e.g., hyper or hypo). To determine the worst post-baseline value, all scheduled and unscheduled test results will be used. For hematology and serum chemistry, frequency tables of potentially clinically significant abnormalities will be provided. For select shift and summary tables such as LFT summaries, one or both of the following approaches may be utilized: 1) Only central laboratory data will be included; 2) Both central and local laboratory data will be included.

All laboratory data (both central and local) will be provided in data listings. Out-of-range laboratory results will be presented in a separate listing with proper flags. Local laboratory data, if available, will also be flagged.

Liver Function Tests

A frequency table and a shift table will be produced to summarize the number and percentage of patients in each of the below categories at any post-baseline time point.

- ALT >1 & ≤3, >3 & ≤5, >5 & ≤8, >8 & ≤20, >20×ULN,
- AST >1 & ≤3, >3 & ≤5, >5 & ≤8, >8 & ≤20, >20×ULN,
- ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤8, >8 & ≤20, >20×ULN,
- ALP > 1.5×ULN,
- Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN

In separate figures, the peak total bilirubin (as multiple of ULN) at any time post-baseline will be plotted against the peak ALT level and (peak AST and the peak AST or ALT levels) at any time post-baseline.

A listing for all patients with abnormal liver function tests, defined as an ALT >3×ULN, AST >3×ULN, or total bilirubin >2×ULN at any time point, will also be provided.

5.11.3. Vital Signs and Physical Examination

For vital signs and body weight and height, descriptive statistics for actual values and change from baseline by visit will be provided for each variable. Vital sign measurements will be presented for each patient in a data listing, with abnormal vital signs flagged.

5.12. Interim Analysis

No formal interim analysis is planned for this study.

5.13. Other Analyses

Additional data are collected to characterize the impact of the COVID-19 pandemic on general study conduct and disposition, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidance (including FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

5.13.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries.

Impact on study participation due to COVID-19, including missing visits, visit location changes, study drug dosing changes and missing doses, will be summarized descriptively overall and by visit on the patient level, and overall on the event level. Patient- and event-level summaries of the impact on study participation due to COVID-19 may also be generated by site and/or region.

Impact on study participation due to COVID-19 will be presented in data listings at patient and visit level.

5.13.2. Impact on Efficacy

COVID-19 pandemic impacted efficacy analyses are not carried out for the primary analysis since efficacy assessments (e.g., blood and urine samples for PD) missed due to COVID-19 pandemic are expected to be minimal.

Given the measures specified in the protocol designed to ensure data integrity, analyses excluding patients with COVID-19 related protocol deviations will not be prespecified, but may be considered post hoc, if warranted.

5.13.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will be presented. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

AEs mapping to the COVID-19 custom query will also be presented in a data listing.

6. CHANGES FROM PLANNED ANALYSES

Below is a summary of changes/clarification from the protocol

SAP Original

Section of the SAP	Summary of change from protocol	Rationale
Section 2.4 and Section 4.5	Added the first 2 valid 24-hour urine collections to the calculation of the mean baseline urinary oxalate level stratification factor.	The addition of the first 2 valid 24-hr urine collections to the stratification mean baseline urinary oxalate improves clarity.
Section 3 and Section 5.8	Plasma Oxalate Analysis Set is added for the analysis of the plasma oxalate endpoint.	The LLOQ of the plasma oxalate assay is 5.55 µmol/L. Due to the inability of quantify oxalate level below LLOQ by the assay, patients with baseline plasma oxalate level measured near to or at LLOQ are excluded from the analysis to ensure the meaningful reduction can be evaluated for the study population.
Section 3	Removed "randomized" from the Safety Analysis Set definition.	"Randomized" was erroneously entered in the protocol.

7. APPENDICES

7.1. Protocol 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										

		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	

		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)**
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	
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

		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)**
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									
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										

		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)**
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; [redacted]
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.

[redacted]

The scoring algorithm for the WISQOL below is transcribed from the WISQOL Scoring [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.3. Imputation for Missing or Partial Dates

All data listings will display missing or partial dates as reported without imputation.

For prior and concomitant medications, missing or partial dates will be imputed to determine prior versus concomitant medications using the following imputation rules:

- For medications with partial start or end dates, the first day/month will be imputed for start date, and the last day/month will be imputed for end date.
- For medications with a completely missing start date, the medications will be considered as started one day prior to the first dose of study drug. If an imputed start date is after the collected end date, the end date will be used as the imputed start date.
- For medications with a completely missing end date or an imputed end date that is after the earliest date of: end of study date, data cutoff date or date of death, the latter (i.e., the earliest date of: end of study date, data cutoff date or date of death) will be used as the imputed end date.

Missing or partial AE onset dates will be imputed to define TEAEs using the following imputation rules:

- AE onset dates with missing day and non-missing month will be imputed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.
- AE onset dates with missing month will be imputed to occur on the first day of the non-missing year (i.e., January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.
- If year of the AE start date is missing, the onset date will be imputed as the first day of dosing, except it can be unequivocally determined (from the partial or complete stop date) that the event occurred prior to the first dose of study drug, in which case the AE onset date will not be imputed.
- If an imputed onset date is after the collected AE end date, the end date will be used as the imputed onset date.

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ALN-GO1-008 SAP Original

Task: Approval Verdict: Approve	[redacted]T+0000
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Task: Approval Verdict: Approve	[redacted]25:27 GMT+0000
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