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STATISTICAL ANALYSIS PLAN

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

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Phase:	Phase 3
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Confidentiality Statement

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

APPROVAL SIGNATURE PAGE

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ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AGT	alanine-glyoxylate aminotransferase
AGXT	alanine glyoxylate aminotransferase gene
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
BMI	Body mass index
BSA	Body surface area
C_{max}	Maximum plasma concentration
CSR	Clinical study report
DB	Double-blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ET	Early termination
EQ-5D	Euro Quality of Life Health State Profile Questionnaire
ESRD	End-stage renal disease
FAS	Full analysis set
GO	Glycolate oxidase
IRS	Interactive response system
ISR	Injection site reactions
KDQOL	Kidney Disease Quality of Life Questionnaire
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect repeated measures
MNAR	Missing not at random

Abbreviation	Definition
PD	Pharmacodynamic
PT	Preferred term
PK	Pharmacokinetics
PedsQL	Pediatric Quality of Life
PH1	Primary hyperoxaluria type 1
QoL	Quality of life
SAP	Statistical Analysis Plan
SOC	System Organ Class
SMQ	Standardized MedDRA Queries
VAS	Visual analog system
ULN	Upper Limit of Normal

1. INTRODUCTION

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disease characterized by excessive oxalate production by the liver and consequent hyperoxaluria. PH1 is caused by mutations in the alanine glyoxylate aminotransferase (*AGXT*) gene, which encodes the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). As a consequence of AGT deficiency, glyoxylate accumulates and is oxidized to oxalate in the hepatocyte and ultimately transported to the kidneys for excretion. Oxalate, in the form of its calcium salt, is excreted almost entirely by the kidney. Due to its insolubility, calcium oxalate can crystallize readily in the urinary tract. In PH1, excess urinary oxalate results in recurrent nephrolithiasis and/or nephrocalcinosis, which can lead to pain, infections, progressive kidney disease and failure, along with reduced quality of life.[Cochat 2013] As renal function declines, elimination of oxalate is further reduced, such that calcium oxalate accumulates in bone, vasculature, skin, retina, heart, and nervous system, resulting in severe end-organ damage.[Cochat 2013] This devastating condition, systemic oxalosis, arises when the estimated glomerular filtration rate (eGFR) has declined to below 30 to 45 mL/min/1.73 m^2.[Cochat 2013]

The ILLUMINATE-A Study (ALN-GO1-003) is a Phase 3 study designed to evaluate the efficacy and safety of SC-administered lumasiran in patients with PH1. This statistical analysis plan (SAP) has been developed based on the protocol of the ILLUMINATE-A study (Amendment 2 dated 19 March 2019).

The analysis methods described in the protocol may be updated in this statistical analysis plan (SAP). Any change to the data analysis methods described in the protocol, as well as the justification for the change, will be described in this SAP (Section 8) and the clinical study report (CSR). Additional exploratory analyses of the data may be conducted when deemed appropriate.

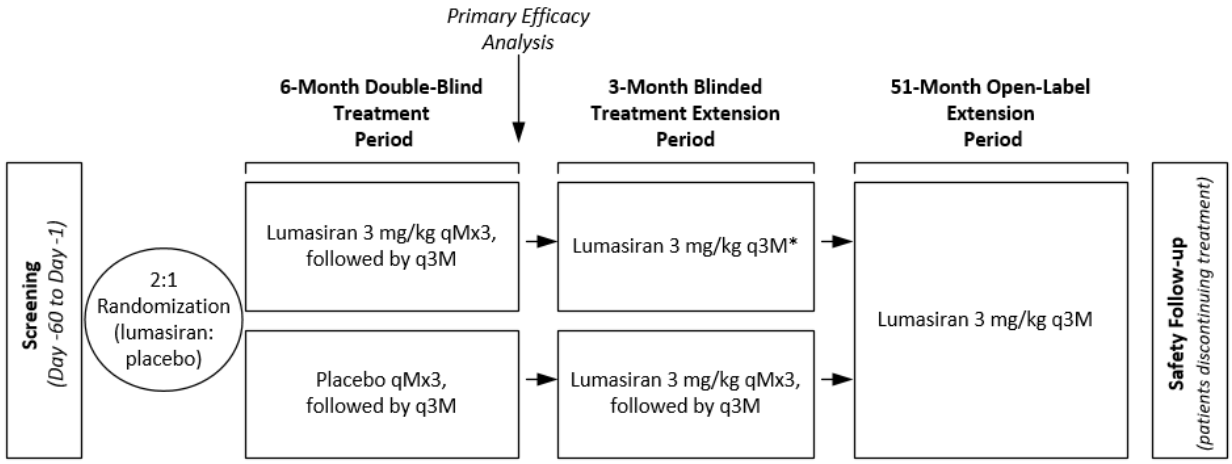
2. STUDY OVERVIEW

2.1. Synopsis of Study Design

The ILLUMINATE-A Study (ALN-GO1-003) is a multicenter, multinational Phase 3 study designed to evaluate the efficacy and safety of lumasiran in approximately 30 patients with PH1; the study is comprised of a 2:1 randomized, double-blind, placebo-controlled period of 6 months, followed by an 3-month blinded treatment extension period and an open label extension period of up to 51 months to evaluate the long-term safety and efficacy of lumasiran.

The study design schema is presented in Figure 1.

Figure 1: Study Design



*To maintain the blind to treatment assignment, study drug will be administered in the same manner and at the same frequency as in the 6-month double-blind period. Patients randomized to lumasiran will also receive 2 qM doses of placebo during the 3-month blinded treatment extension.

2.2. Randomization Methodology

Patients will be randomized 2:1 to receive either lumasiran or placebo in a double-blind manner. Treatment will be stratified at randomization based upon mean 24-hour urinary oxalate level from the first 2 valid samples collected during screening (≤1.70 mmol/24hr/1.73m^2 vs. > 1.70 mmol/24hr/1.73m^2).

2.3. Blinding

Treatment assignments will be maintained by the interactive response system (IRS). Any unplanned unblinding occurring during the 6-month double-blind placebo-controlled treatment period will be documented and reported in the CSR.

Alnylam and all sponsor personnel (except for staff involved in study drug supply, eTMF and study drug supply) will also be blinded to treatment assignments and laboratory results until the interim database lock for the primary analysis of the 6-month double-blind treatment period.

Investigators and all site personnel will be blinded to treatment assignments and laboratory results that could potentially unblind them (e.g., 24-hour urinary oxalate, 24-hour urinary glycolate, plasma oxalate, plasma glycolate, spot urinary oxalate, spot urinary glycolate, renal ultrasound, pharmacokinetics (PK), antidrug antibody (ADA) until the last patient completes the assessments at the Month 9 visit.

Details regarding the blinding aspects during the study are outlined in a Randomization and Blinding Plan for ALN-GO1-003. The plan defines blinded data sources, identifies roles and responsibilities of study team members at Alnylam (or external) with their access (if any) to blinded data sources and addresses actions to be taken if a potentially unblinding event occurs prior to the interim database lock for the primary analysis of the 6-month double-blind treatment period in order to preserve the integrity of this study.

An independent, external data monitoring committee (DMC) and an independent, external biostatistics group supporting the DMC will have access to subject level data treatment assignments and blinded data sources throughout the study.

To identify irregular and potentially erroneous results of PK a pharmacodynamic (PD) data from blinded data sources prior to unblinding, a clinical pharmacologist independent of the study team reviews the listings of such data with dummy subject ID (i.e., no link to other clinical data) and communicates the findings to unblinded personnel at a clinical research organization for issue resolution.

2.4. Study Procedures

The schedule of assessments is described in the study protocol (Table 1 and Table 2). Testing on PD samples for the study endpoints is performed at [redacted] using validated PD assay.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

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

3.1.2. Secondary Objectives

- To characterize the effect of lumasiran on absolute levels of urinary oxalate excretion, urinary oxalate: creatinine ratios, and plasma oxalate
- To evaluate the long-term effect of lumasiran
- To evaluate the effect of lumasiran on renal function

3.1.3. Exploratory Objectives

- To evaluate quality of life (QoL)
- To evaluate the change in nephrocalcinosis and renal stones
- To evaluate additional pharmacodynamic (PD) parameters of plasma glycolate, urinary glycolate and urinary oxalate in spot urine collections
- To characterize the Pharmacokinetics (PK) of lumasiran
- To assess for antidrug antibodies (ADA) against lumasiran
- To evaluate the effects of lumasiran on patient and caregiver resource use
- To describe the patient experiences on lumasiran in PH1 Patients and the experiences of caregivers for these patients

3.1.4. Safety Objective

- To evaluate the safety and tolerability of lumasiran in patients with PH1

3.2. Endpoints

3.2.1. Primary Endpoint

Percent change in 24-hour urinary oxalate excretion from baseline through Month 6 corrected for body surface area (BSA).

3.2.2. Secondary Endpoints

- Absolute change in 24-hour urinary oxalate corrected for body surface area (BSA) from baseline to Month 6
- Percent change in 24-hour urinary oxalate: creatinine ratio from baseline to Month 6
- Percent change in plasma oxalate from baseline to Month 6
- Proportion of patients with 24-hour urinary oxalate level at or below 1.5xULN at Month 6
- Proportion of patients with 24-hour urinary oxalate level at or below ULN at Month 6
- Absolute change in plasma oxalate from baseline to Month 6
- Change in in estimated glomerular filtration rate (eGFR) from baseline to Month 6
- Change from baseline (percent and absolute) 24-hour urinary oxalate excretion, percentage of time that 24-hour urinary oxalate is ≤1.5 × ULN, 24-hour urinary oxalate: creatinine ratios and eGFR in the extension periods

3.2.3. Exploratory Endpoints

- Change in Kidney Disease Quality of Life Questionnaire (KDQOL) for patients ≥18 years of age at screening, and the Pediatric Quality of Life Inventory (PedsQL) [the generic and ESRD modules]) for patients <18 years of age at screening
- Change in Euro Quality of Life Health State Profile Questionnaire (EQ-5D) and EQ-5D Visual Analog Scale (VAS)
- Change in rate of renal stone events
- Change in nephrocalcinosis as assessed by renal ultrasound
- Change in urinary and plasma glycolate
- Change in urinary oxalate: creatinine ratios as assessed in random spot urine collections
- PK profile of lumasiran
- Frequency of ADA

- Change in patient resource use (e.g., work/school attendance, visits to doctor/hospital)
- Change in patient experiences as evaluated by a patient and caregiver experience survey

3.2.4. Safety Endpoints

The primary safety parameter is frequency and seriousness of adverse events (AEs) during the double-blind treatment period and in the extension periods.

Other safety parameters also include vital signs (including height and weight), 12-lead ECGs, clinical laboratory assessments, and physical exams. Renal stone events are defined in the protocol efficacy assessments and will not be included in any safety summaries of AEs and/or SAEs.

4. PATIENT POPULATION

4.1. Patient Definitions

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- Safety Analysis Set: All patients who received any amount of study drug. Patients will be analyzed according to the treatment actually received.
- PK Analysis Set: All patients who received any amount of study drug and have at least 1 PK concentration measurement.
- All Lumasiran Treated Set: All patients who received any amount of lumasiran, including patients who took lumasiran during the 6-month double-blind period and patients who initially took placebo during the 6-month double-blind period and then switched to lumasiran during the extension period.
- Plasma Oxalate Analysis Set: All patients who received any amount of study drug and have a baseline plasma oxalate level ≥ 1.5*LLOQ

The primary population used to evaluate efficacy will be the Full Analysis Set (FAS) for the primary and secondary endpoints during the 6-month double-blind period. Safety during the double-blind period will be analyzed using the Safety Analysis Set. The PK Set will be used to evaluate the PK endpoints. The All Lumasiran Treated Set will be used to summarize the long-term efficacy and safety of lumasiran. The Plasma Oxalate Analysis Set will be used to evaluate the endpoints for the change from baseline in plasma oxalate.

4.2. Protocol Deviations

Protocol deviations will be classified into major or minor deviations by medical review. A major deviation is defined as a deviation that may significantly impact the completeness, accuracy

and/or reliability of the trial data; that may significantly affect a patient's rights, safety and well-being (ICH.E3 R1 Structure and Contents of Clinical Study Reports Guidance for Industry. 2013). Deviations not classified as major will be assigned as minor. Major protocol deviations will be reviewed and approved by Alnylam prior to the interim database lock for the primary analysis of the 6-month double-blind treatment period and unblinding of treatment assessment for all patients. All protocol deviations will be presented in a listing.

The Sponsor or designee will be responsible for producing the final protocol deviations file. This file will include at a minimum each protocol deviation and whether or not this deviation is classified as a major protocol deviation. This file will be finalized prior to the primary treatment phase database lock and study unblinding.

Protocol deviations will be summarized in the clinical study report.

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

The planned total enrollment for the study is approximately 30 patients.

Twenty-four patients will yield 90% power to detect a treatment difference of 37% at a 2-sided 5% significance level assuming the mean percent reduction from baseline to Month 6 in 24-hour urinary oxalate corrected for BSA is 17% with a standard deviation (SD) of 25% in the placebo arm, and a mean percent reduction from baseline to Month 6 in 24-hour urinary oxalate corrected for BSA of 54% with SD of 25% in the lumasiran arm.

5.2. General Methods

Continuous data will be described using descriptive statistics such as the number of observations (n), mean, standard deviation, standard error, median, quartiles, minimum, and maximum. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Median and mean will be presented to the level of precision collected in database plus one additional decimal. Standard deviation and standard error will be presented to the level of precision collected in the database plus 2 additional decimals.

For assessments with repeated collections at a given study visit (e.g. ECG parameters, height for ages<18 years old), the mean will represent the value at the visit for all parameters except for 24-hour urine PD parameters. For 24-hour urine PD parameters, if there are any repeated collections at a visit, then the median will represent the value at that visit. For biomarker and/or lab data, if any value is recorded as <lower limit of quantification (LLOQ) then the assigned value used for calculations of summary statistics will be assigned a value of the LLOQ.

Categorical and ordinal data will be described using the patient count and percentages in each category. When count data are presented, the percentage will not be presented when the count is zero.

Tables and figures will primarily summarize data during the double-blind period and during lumasiran treatment. These time periods are defined directly below. In addition, there will be a subset of tables and figures for efficacy endpoints which will also summarize by protocol defined study visit across the entire study for patients in the FAS set.

During the Double-Blind (DB) Period: defined as the time period prior to the first study drug dose date/time in the extension period (e.g. date/time of lumasiran dose at month 6).

Tables and figures will be presented by treatment arm (lumasiran or placebo). For safety summaries (i.e. AEs, Labs, ECGs, VS, etc.), all assessments up to the date/time of the first dose in the extension period (i.e. date/time of lumasiran at month 6) or, for patients not dosed in the extension period, all assessments collected within 84 days of the last dose of study drug will be included. For efficacy summaries, all data up to and including the month 6 visit will be presented.

Extension Period: defined as the period starting on/after the first date/time of lumasiran at month 6 (i.e. start of the 3-month blinded treatment extension period).

During Lumasiran treatment: defined as the time period during which patients receive lumasiran (i.e. on or after the first date/time of lumasiran until 84 days after the last dose of lumasiran). Baseline and study days will be relative to the first dose of lumasiran and will be re-derived for patients initially randomized to placebo (Section 5.4 and Section 5.8).

Summary tables and figures will be presented by treatment sequence (lumasiran/lumasiran, placebo/lumasiran and all lumasiran treated). Both safety and efficacy summaries will include all assessments during lumasiran treatment (i.e. any assessment collected on or after the first dose until 84 days after the last dose of lumasiran).

Per-patient listings will include all data collected during the entire study. The listings will be sorted by randomized arm. Within patient, there will be a variable to indicate the period of the data collection.

Day 1 will be defined as the day of the first dose of study drug (lumasiran or placebo). Day is relative to first dose date of study drug for all patients:

If the assessment date is after the date of first study drug dose, then the study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug + 1

If assessment date is before the date of the first dose of study drug, then study day will be calculated as:

Study Day = Date of assessment – date of first dose of study drug

For patients who were randomized to placebo but later received lumasiran, these patients will have additional variables displayed in listings to reflect the data collected relative to the first dose of lumasiran. At a minimum, all listings will include two sets of definitions for the following variables:

- Baseline: relative to first randomized dose of placebo and relative to first dose of lumasiran (Section 5.4).
- Study Day: relative to first randomized dose of placebo and relative to first dose of lumasiran.
- Visit: based upon actual study visits and visits re-aligned relative to first dose of lumasiran (Section 5.8).

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints evaluated during the DB period (except eGFR as this endpoint is not expected to change within six months). Testing will be conducted at the nominal 2-sided 0.05 level of significance. Secondary endpoints will be tested in a prespecified hierarchy (Section 5.6). Summary statistics will be presented, as well as 2-sided 95% confidence intervals on selected parameters, as described in the sections below.

All data recorded on the CRF will be displayed in data listings.

5.3. Computing Environment

All statistical analyses will be performed using validated SAS statistical software Version 9.4 (or later), unless otherwise noted.

5.4. Baseline Definitions

Baseline definitions applied to double-blind (DB) period:

For 24-hour urine PD parameters, baseline will be defined as the median of all valid 24-hour urine PD parameters collected prior to the first dose date/time of study drug (lumasiran or placebo). Baseline for other PD parameters will use the mean of all measurements collected prior to the first dose date/time of study drug (lumasiran or placebo).

For other parameters, baseline is defined as the last non-missing value prior to the first dose date/time of the study drug (lumasiran or placebo), unless otherwise specified. The baseline value for any measurements with multiple values at a visit (e.g. ECGs, height and weight for patients <18 years old) will be defined as the mean of the latest values collected prior to the first dose date/time of study drug.

Baseline definitions applied to During Lumasiran Treatment:

For patients randomized to lumasiran, baseline as defined above for the double-blind period will be used.

For patients randomized to placebo who took at least one dose of lumasiran in the extension period, baseline for all parameters [except for 24-hour urine PD parameters] will be defined as above but the date of the first dose date/time of study drug will be the first date/time of lumasiran dose. For 24-hour urine PD parameters, the baseline will be defined as the median of all valid assessments at month 6. If the subject does not have two valid 24-hour urine PD assessments at month 6, then the baseline will be calculated based on the latest three valid 24-hour urine PD collections prior to the first dose date/time of lumasiran.

5.5. Randomization Stratification Factors

The mean 24-hour urinary oxalate excretion (≤1.70 mmol/24h/1.73m^2 or >1.70 mmol/24h/1.73m^2) from the first 2 valid 24-hour urine collections during screening will be the stratification factor. The stratification factor will be recorded in both the IRS (Interactive Response System) and the clinical database.

The central laboratory for the 24-hour urinary oxalate measurements used for randomization during screening was transitioned from [redacted] (i.e., Clinical Assay) to [redacted] (i.e., Validated PD assay). As a result, the first 5 subjects were stratified using the results based on the Clinical Assay [redacted] and the remaining patients were stratified using the results based on the Validated PD Assay [redacted].

The planned statistical methods will adjust for baseline 24-hour urinary oxalate (refer to Section 5.4 and Section 7.1) and may not match the stratification factors as recorded in IRS. Any discrepancies will be summarized.

5.6. Multiple Comparisons/Multiplicity

The family-wise Type I error control for the primary and secondary endpoints will be achieved by the gatekeeping testing strategy. Once the primary hypothesis testing is statistically significant at a 2-sided 0.05 significance level, the secondary endpoints will be tested in the following hierarchical order.

1. Absolute change in 24-hour urinary oxalate corrected for BSA from baseline to Month 6
2. Percent change in 24-hour urinary oxalate: creatinine ratio from baseline to Month 6
3. Percent change in plasma oxalate from baseline to Month 6
4. Proportion of patients with 24-hour urinary oxalate levels at or below 1.5xULN at Month 6
5. Proportion of patients with 24-hour urinary oxalate levels at or below ULN at Month 6
6. Absolute change in plasma oxalate from baseline to Month 6

Only if the comparison is significant at a 2-sided 0.05 significance level will the next endpoint in the hierarchy be formally tested; if a given comparison is not significant at a 2-sided 0.05 significance level, the subsequent tests will be performed, and the results will be summarized, but statistical significance will not be inferred.

5.7. Missing Data

Patients who discontinue the study prior to Month 6 will be encouraged to remain on study and complete their remaining clinical visits (excluding PK assessments) through the visit at Month 6 and only safety follow-up visits afterwards. All data collected regardless of whether it was collected before or after treatment discontinuation will be used for analysis. However, it is possible that data will remain missing.

An AE will be considered 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 first dose of study drug.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug in this study; medications will be classified as prior or both prior and concomitant depending on the medication stop dates. If any medications have a completely missing stop date, then the medication will be assumed as ongoing.

5.8. Visit Windows

For table and figure summaries of the DB period, all data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report forms (eCRF) even if the assessment is outside of window.

For table and figure summaries of the during lumasiran treatment, the data collected at study visits during the extension period will be re-mapped for the patients randomized to placebo to reflect the visit relative to the first dose of lumasiran (e.g. Month 7 re-mapped to Month 1), Month 8 re-mapped to Month 2, etc.).

Unless otherwise specified, data collected at an unscheduled visit will be included in by patient listings and/or spaghetti plot figures, but no assignment of the scheduled visit will be made for the purposes of summary tabulations. However, unscheduled study visits will be used in the calculation of baseline values and for the any categorical shift tables (e.g. shift from baseline to worst post-baseline value).

5.9. Interim Analysis

There will not be an interim analysis prior to the primary analysis of the 6-month double blind period which will occur when the last patient completes the 6-month visit. There may be interim analyses conducted after the 6-month double-blind period to support regulatory and/or publications requests.

5.10. Analysis for Primary Endpoint and Database lock

As this study will be ongoing at the time of the primary analysis, the study database will have an interim database lock occur (i.e. data in EDC will be frozen and external data such as laboratory data will be QA'd and cleaned) when the last patient completes the 6-month visit to conduct the primary analysis of the double-blind period. Additional details regarding the interim database lock are located in the study Data Management Plan. The study will then be unblinded and all data entered as of the date of the primary treatment phase database lock will included in the summary of the Clinical Study Report (CSR).

After the study is completed (i.e. all patients complete the long-term open-label extension period and/or required safety follow-up visit(s)), the database will be hard locked, and all data will be summarized in the updated CSR.

6. STUDY ANALYSES

6.1. Patient Disposition

Number and percentage of patients will be tabulated for the following categories:

- Screen Failures
- Enrolled (signed informed consent and met eligibility)
- Randomized
- Treated
- Full Analysis Set (FAS)
- Safety Analysis Set
- PK Analysis Set
- All Lumasiran Treated Set
- Plasma Oxalate Analysis Set

Summaries of the number and percentage of patients who discontinued treatment, withdrew from study, and primary reasons for either discontinuation of treatment and/or withdrawal from study will be presented. Additionally, the number of patients who completed the month 6 visit will also be displayed. A patient is defined as having completed the month 6 visit if the patient has at least one valid 24-hour urinary oxalate corrected for BSA at that visit.

The number and percent of patients enrolled by country and site will be summarized by randomized arm and overall. The number and percent of patients in each randomization stratum recorded in IRS vs. clinical database will also be summarized by randomized treatment arm and overall.

Data listings of those patients who withdrew and/or discontinued treatment including the associated reasons will also be presented. A separate listing of screening failure patients with the associated reason for screen failures will be generated.

6.2. Demographics and Baseline characteristics

Descriptive statistics of demographic characteristics including but not limited to: age (years), age category (6 to <12, 12to <18, ≥18 to <65 and ≥65), gender, race, ethnicity, region, height, weight, BSA, and body mass index (BMI) will be presented. For patients <18 years at screening, modified z-scores for height, weight and body mass index will also be summarized.

Additional disease baseline characteristics including but not limited to: 24-hour urinary oxalate excretion corrected for BSA (mmol/24hours/1.73m^2), 24-hour urinary oxalate: creatinine ratio, eGFR (mL/min/1.73m^2), plasma glycolate (µmol/L), plasma oxalate (µmol/L), and total number of patients reported with vitamin B6 use prior to study entry will be summarized using descriptive statistics.

A tabular summary of historical disease characteristic information such as: age at diagnosis, time from diagnosis to first dose date (months), time from first symptoms to first dose date (months),

time from diagnosis to first symptoms (months), number of siblings with PH1, reported history of disease events (e.g. pyelonephritis, renal stones, kidney stones, urinary tract infection), and genotype will also be presented.

6.3. Medical History

A complete medical and surgical history will be collected during screening. The medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 21.1 or higher).

Medical and surgical history will be summarized for the Safety Analysis Sets by system organ class, high level term and preferred term.

6.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2018 or later). Prior medications are defined as medications that were taken prior to and stopped before the first dose of treatment (lumasiran or placebo). Concomitant medications are defined as medications which were taken prior to and were ongoing while on study drug or medication(s) taken on or after the first dose date of the study drug.

Tabular summary of the number and percentage of subjects taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term. Data will be presented for the Safety Analysis Sets. A separate tabular summary of Prior Vitamin B6 and Concomitant Vitamin B6 use will be summarized by ATC and preferred term.

One subject/patient listing for prior medication/concomitant medications and a separate listing for prior and concomitant vitamin B6 medications will be generated.

6.5. Dosing and Extent of Exposure

Summaries of exposure will include the following categories such as, but not limited to: total number of doses received per patient, mean number of dosing per subject, cumulative number of doses received, duration of drug exposure (months), cumulative drug exposure time (months), the total dose administered (mg) and total volume administered (mL).

Definition of drug exposure (days) will be defined as the minimum of [Exposure time= (date of last exposure – date of first dose +1)] where date of last exposure will represent either the date of the last dose administered dose +84, analysis cut-off date or end of study date. The exposure during the DB period will be right censored; that is, the date of the last exposure will not be later than the first date of dosing in the Extension period.

Dose interruptions and compliance are not taken into account.

7. STATISTICAL ANALYSIS

7.1. Primary Endpoint

The primary endpoint of this study is the percent change from baseline to Month 6 in 24-hour urinary oxalate corrected for body surface area (BSA). The primary comparison between the randomized arms is based on the percent changes at months 3, 4,5, and 6 from baseline. The analysis will be conducted using the Full Analysis Set.

24-hour urinary oxalate (mmol/24hrs/1.73m^2) corrected for BSA at each visit per patient is calculated as follows:

[Urine oxalate concentration (umol/L)/1000 (umol/mmol)] * [24hr urine volume (mL)/1000 (mL/L])] * [24 hours/actual collection hours] * [1.73/(BSA)]

where BSA=square root (mean height (cm)*weight (kg)/3600) at the visit.

Only valid 24-hour urinary oxalate values will be included in the analysis (note: valid is defined as: creatinine ≥10.0 mg/kg, duration of collection 22 to 26 hours, no missing voids and the sample was not collected within 14 days after the most recent dialysis session, if applicable).

The primary analysis will be performed using a restricted maximum likelihood (REML) based Mixed-Effect Model Repeated Measures (MMRM) approach. The outcome variable is percent change from baseline in 24-hour urinary oxalate corrected for BSA (mmol/24hr/1.73m^2) at months 3, 4, 5, and 6. Analysis will include fixed effects of treatment arm (lumasiran vs. placebo) and scheduled visits (months 3, 4, 5 and 6), as well as continuous, fixed covariate of baseline 24-hour urinary oxalate corrected for BSA (mmol/24hr/1.73m^2) level and patient as a random factor. The treatment estimates from this model will represent an average percent change from baseline of 24-hour urinary oxalate excretion across months 3 through 6 at which the treatment effect is expected to have reached steady state. Furthermore, given the variability of 24-hour urinary oxalate, averaging the values across these visits will yield stable treatment estimates. An unstructured covariance structure matrix will be used to model the within-patient error. If the fit of the unstructured covariance structure matrix fails to converge, then the following covariance structures will be assessed: autoregressive (1), compound symmetry, and Toeplitz and the structure selected will be based upon the best fit chosen by Akaike Information Criteria (AIC). The Satterthwaite approximation will be used to estimate denominator degrees of freedom. At each visit, least square (LS) means with corresponding standard errors (SEM) and 95% confidence intervals (CI) will be displayed by treatment arm. The primary comparison is the LS mean treatment difference (lumasiran – placebo) in percent change from baseline of 24-hour urinary oxalate excretion from months 3 to 6. This LS mean difference will be presented along with corresponding standard errors (SEMs), 95% CIs and p-value from the model.

Descriptive statistics will also be generated by treatment arm at each scheduled visit. LS Mean (+/- SEM) figures of percent reduction by treatment arm will be plotted as well as individual spaghetti plots. A table of the mean maximum percent reduction during the 6-months for each treatment arm will also be generated. It should also be noted that the primary measure (i.e., 24-hour urinary oxalate corrected for BSA), as well as other PD markers, is based on validated PD assay [redacted].

7.1.1. Sensitivity Analysis

Sensitivity analysis will be conducted to evaluate the sensitivity to the estimated treatment effect by the assumption of lumasiran reaching steady state of the treatment effect at month 3 and maintained through month 6.

- Sensitivity analysis 1 estimates the treatment effect of the primary endpoint without assuming equal treatment effect from month 3 through month 6. The analysis adds the interaction of visit and treatment to the primary MMRM model, when month 3 through month 6 data are used.
- Sensitivity analysis 2, similar to sensitivity analysis 1, estimates the treatment effect of the primary endpoint without assuming equal treatment effect from month 3 through month 6, but including all post-baseline data (including percent change from baseline at months 1 and 2)).

Table 1: Analyses of the Primary Endpoint

Analysis	Analysis Set	Statistical model	Data[1]
Primary analysis	Full Analysis Set	MMRM (subject, baseline, treatment, visit)	M3, M4, M5, M6
Sensitivity Analysis 1	Full Analysis Set	MMRM (subject, baseline, treatment, visit, treatment*visit)	M3, M4, M5, M6
Sensitivity Analysis 2	Full Analysis Set	MMRM (subject, baseline, treatment, visit, treatment*visit)	M1, M2, M3, M4, M5, M6

[1]Percent change from baseline in 24-hour urinary oxalate corrected for BSA at each month (M) to be used in the model.

7.2. Secondary Endpoints

For secondary endpoints assessed to Month 6, the analysis will compare randomized arms (lumasiran vs. placebo) using the Full Analysis Set. During the Double-Blind Period, data will be collected during Screening, Day 1 and Months 1, 2, 3, 4, 5 and 6 with the exception of eGFR which is also collected at Week 2. To control for type I error, the primary and selected secondary endpoints will be tested in a hierarchical order as described in Section 5.6.

Absolute change from baseline in 24-hour urinary oxalate corrected for BSA will be analyzed using an MMRM model as specified for the primary endpoint. The percent change in 24-hour urinary oxalate: creatinine ratio, the percent change and the absolute change in plasma oxalate from baseline to Month 6 will also be analyzed using a similar MMRM model to the primary endpoint with the exception being that the baseline variable will be the baseline value of the corresponding endpoint.

For the two plasma oxalate related endpoints, a separate enriched analysis set of patients (i.e., Plasma Oxalate Analysis set) will be used. The plasma oxalate analysis set is defined as those patients who received any amount of study drug and have a baseline plasma oxalate level ≥ 1.5*LLOQ. The LLOQ of the plasma oxalate assay is 5.55 µmol/L. [redacted] Because it is not

possible to quantify plasma oxalate levels below LLOQ using the assay, patients with baseline plasma oxalate levels near the LLOQ (i.e. <1.5*LLOQ) are excluded from the analysis to ensure that meaningful reductions in plasma oxalate can be evaluated for the study population.

For binary endpoints, i.e., the proportion of patients with 24-hour urinary oxalate ≤1.5 ULN and ≤ ULN at Month 6 the number and associated percent of patients who met each threshold at Month 6 will be presented by treatment arm. Refer to Appendix A for the value of ULN. Binary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline urinary oxalate (≤1.70 mmol/24hr/1.73m^2 vs. >1.70 mmol/24hr/1.73m^2). The odds ratio with the corresponding 95% confidence interval and associated p-value will be presented. In addition, the differences in proportion of responders and corresponding 95% confidence interval using the Newcombe method based on the Wilson score will also be presented.

For continuous endpoints (including eGFR), descriptive statistics will be generated by treatment arm. LS Mean (+/- standard error) by treatment arm will be plotted for continuous PD endpoints. Spaghetti plots will also be generated for all continuous endpoints.

Table 2: Analysis of Secondary Endpoints to Month 6^

Endpoints	Statistical Method	Analysis Population
Absolute change in 24-hour urinary oxalate to Month 6	MMRM	Full Analysis Set
Percent change in 24-hour urinary oxalate:creatinine ratio to Month 6	MMRM	Full Analysis Set
Percent change in plasma oxalate from baseline to Month 6	MMRM	Plasma Oxalate Analysis Set
Proportion of Patients with 24-hour urinary oxalate ≤1.5xULN at Month 6	CMH	Full Analysis Set
Proportion of Patients with 24-hour urinary oxalate ≤ULN at Month 6	CMH	Full Analysis Set
Absolute change in plasma oxalate from baseline to Month 6	MMRM	Plasma Oxalate Analysis Set

^eGFR will be summarized descriptively (i.e. no formal testing) because this endpoint is not expected to change during the 6 months.

The following secondary endpoints which are assessed beyond Month 6 will be summarized to demonstrate long-term durability of lumasiran using the All Lumasiran Treated Set.

Descriptive statistics of percent change in 24-hour urinary oxalate at and after 6 months of lumasiran will be presented by treatment sequence (lumasiran/lumasiran, placebo/lumasiran) and the all treated arm (pooling treatment arms). A Wilcoxon-signed rank test (2-sided) will be conducted to test the null hypothesis of no change from baseline at selected timepoints (Months 6, 12, 18, 30, 36, 42 and 54). Additionally, the mean percent change from baseline with associated 95% (CIs) confidence intervals at each selected timepoint will also be presented. Supportive figures of mean (+/-standard error) percent change will be generated.

Descriptive statistics of percent change in 24-hour urinary oxalate will also be generated at visits during the entire study using the FAS set. Supportive figure of mean (+/- standard error) percent change will also be generated. An analysis of the percentage of time that 24-hour urinary oxalate level is at or below the near-normalization threshold will be summarized. A patient is considered to have met the threshold if the 24-hour urinary oxalate level is ≤1.5xULN at a post-baseline visit.

For each patient, the percentage of time that 24-hour urinary oxalate level is at or below the near normalization threshold (ie, ≤1.5xULN) will be calculated as follows:

$$\frac{cumulative\ months\ at\ or\ below\ near\ normalization\ threshold}{cumulative\ months\ of\ valid\ assessments} \times 100$$

where cumulative months at or below the near normalization will be defined as the summation across all intervals that met the threshold and cumulative months of valid assessments will be defined as the summation across all valid post-baseline collections.

Given that the sample collection varies during the study (e.g. monthly up until M9, every 3 months until M24, every 6 months until Month 60), the calculation will take into account the following considerations:

- Time will be restricted to a maximum of 36 months on lumasiran (that is, up to protocol defined month 36 visit for lumasiran/lumasiran arm or up to protocol defined month 42 visit for placebo/lumasiran arm) or premature treatment discontinuation, whichever occurs first.
- A linear interpolation method will be used for to determine the bookend dates at which the patient crossed into the threshold and crossed out of the threshold.

Descriptive statistics of percentage of time at or below the threshold (among the subset of patients who had at least one post-baseline value which met threshold) will be presented for each treatment sequence arm and the all treated arm. In addition, the number of patients and associated percentage of patients in each category (e.g. <25%, ≥25% to <50%, ≥50% to <75%, ≥75% to 100%) will also be presented.

Descriptive statistics of eGFR at and after 6 months of lumasiran will be presented. Shift tables of eGFR categories from baseline to post-baseline visits and an overall worst post-baseline will also be generated.

7.3. Subgroup Analysis

Subgroup analyses will be conducted to assess the consistency of the treatment effect during the double-blind period for the primary endpoint within the following subgroups:

- Age (6-11, 12 to 17 vs. ≥18 years at screening)
- Gender (Male vs. Female)
- Race (White vs. Non-White)
- Baseline 24-hour urinary oxalate corrected for BSA (≤1.70 mmol/24h/1.73m^2 vs. (>1.70 mmol/24h/1.73m^2)

- Baseline eGFR (≤60 vs. >60)
- History of renal stones (Yes vs. No)
- Baseline vitamin B6 use (Yes vs. No)
- Region 1 (North America [including US and Canada] vs. Other (outside of North America)).
- Region 2 (Europe vs. Other (outside of Europe))

Other subgroups may be examined, if deemed appropriate.

Subgroup analyses will be performed for the primary endpoint of percent change in 24-hour urinary oxalate corrected for BSA to Month 6 using the FAS population. A forest plot will be generated to illustrate the estimated treatment effect along with the associated 95% confidence interval. If the number of patients in a subgroup for either arm is less than 5 patients, then only descriptive statistics will be generated.

The subgroup analyses may be performed for secondary endpoints.

7.4. Exploratory Analysis

Exploratory endpoints will compare lumasiran versus placebo during the DB period using the Full Analysis Set. These endpoints will also be summarized during the long-term efficacy of lumasiran by treatment sequence arms (lumasiran/lumasiran, placebo/lumasiran) and all treated arm (pooling treatment sequence arms) using the All Lumasiran Treated Set.

For changes in PD parameters (urinary oxalate: creatinine ratios as assessed in random spots, plasma glycolate, 24-hour urinary glycolate: creatinine ratio, and urinary glycolate: creatinine ratios as assessed in random spots), descriptive statistics will be presented by visit.

To understand the treatment effect of lumasiran on kidney function, changes over time in renal stone events (as per section 6.3.3. in the protocol) and nephrocalcinosis will be explored.

To evaluate changes in renal stones, protocol defined events will be collected continuously during the study (i.e. renal stone event defined as at least one of the following: visit to heath care provider because of a renal stone, medication for renal colic, stone passage and macroscopic hematuria due to a renal stone). The total number of patients with a renal stone event, total number of renal stone events, total person-days at risk and rate of renal stone events during the respective period (i.e. DB period or during lumasiran treatment) will be presented. The rate will be calculated as total number of renal stone events divided by total person-days at risk during the respective period.

To evaluate changes in nephrocalcinosis, a renal ultrasound will be performed at baseline and at Months 6, 12, 24, 36 48 and 60. The renal ultrasound will also measure the number of kidney stones, the size of the kidney stones, report the location of kidney stones and grade the nephrocalcinosis (range: 0 to 3) where a higher grade indicates greater severity. Changes in the grade of nephrocalcinosis for each kidney (right or left) will be categorized into 3 groups (‘no change’, ‘improving’, and ‘worsening’). At each post-baseline visit, the number and associated percentage of patients in the following 4 categories of the overall change (i.e., accounting for

both kidneys),'no change', 'improving', 'worsening', and 'indeterminate (one kidney improving and one worsening',. will be presented. Descriptive statistics will also be generated.

To explore changes in Quality of Life (QoL), patient resource use and patient experience (or caregiver experience) questionnaires will be collected at baseline and every 6 months during the course of the study.

Changes in patient resource use and/or patient experience (or caregiver experience) will be summarized descriptively.

The QoL instrument will be based upon the age of the patient at screening and the instrument will be used consistently throughout the study. Table 3 outlines the QOL instruments to be collected based upon age at screening.

Table 3: QOL instruments by Age at Screening (<18 years old vs. ≥ 18 years old)

Age at Screening	QOL Instruments	Domains/Subscales	Notes
≥18 years old	EQ-5D-5L	5 domains (5 ordinal levels per domain): mobility, self-care, usual activities, pain/discomfort and anxiety/depression 1 scale: Visual Analogue Scale Score 1 summary score: Index Score (representing health state utility for an average individual with the same combination of per-domain responses as the trial participant in question)	VAS is a common variable in both instruments
<18 years old	EQ-5D-Y	5 domains (3 ordinal levels): mobility, looking after myself, doing usual activities, pain/discomfort and feeling worried/sad/unhappy 1 scale: Visual Analogue Scale Score	
≥18 years old	KDQOL-36	5 subscales: SF-12 Physical Component Summary Score, SF-12 Mental Component Summary Score, Symptoms/Problems, Effects of Kidney Disease and Burden of Kidney Disease	No common variables
<18 years old	PedsQL	4 domains: Physical Functioning, Emotional Functioning, Social Functioning and School Functioning 3 summary scores (total score, physical health summary score and psychosocial health summary score)	
<18 years old	PedsQL ESRD	7 domains: General Fatigue, About My Kidney Disease, Treatment Problems, Family and Peer Interaction, Worry, Perceived Physical Appearance, and Communication 1 summary score: Total Score	

As shown in Table 3, the EQ-5D will be collected to measure general health status in both pediatrics and adult patients with PH1. The VAS and Index Score will range from 0 to 100 where lower values represent a worse quality of life.

During the double-blind period, the change from baseline to month 6 in VAS (pooling: EQ-5D-5L and EQ-5D-Y) will be summarized by randomized treatment arm (lumasiran or placebo),

For the EQ-5D instrument, categorical summaries of the percentage of patients reporting ordinal responses for each of the 5 domains will be presented. Descriptive statistics of actual and change in VAS and Index score (applies to only EQ-5D-5L) will also be generated.

In addition, KDQOL-36 will be collected for adult patients to assess kidney disease specific measures and PedsQL will be collected for pediatric patients to further assess quality of life. In both instruments, values range from 0 to 100 and lower scores indicate a worse self-reported QoL. Descriptive statistics will be generated for each instrument.

7.5. Pharmacodynamic Analysis

Analyses of secondary endpoints relating to 24-hour urinary oxalate corrected for BSA and 24-hour urinary oxalate: creatinine levels are described in Section 7.2 and Section 7.3. Analyses of exploratory PD endpoints (urinary oxalate: creatinine ratios as assessed in random spots, plasma glycolate, 24-hour urinary glycolate: creatinine ratio, and urinary glycolate: creatinine ratios as assessed in random spots) are described in Section 7.4.

7.6. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

Population PK analysis is planned for all patients in the study and will be described in a separate population PK analysis plan.

7.7. Safety Analyses

Primary safety analyses will compare lumasiran versus placebo during the DB period using the Safety Analysis Set. Long-term safety analyses of lumasiran will be summarized by treatment sequence (lumasiran/lumasiran, placebo/lumasiran, all treated arm) using the All Lumasiran Treated Set.

The safety analyses will be based upon treatment received (i.e. if a patient receives at least one dose of lumasiran, then he/she will be included in the lumasiran arm).

The primary safety parameter is treatment emergent Adverse Event (AEs) which will be defined as an AE that occurs or worsens on or after the first dose date/time of study drug though 84 days after the last dose of study drug. In addition, any AE that worsened in intensity or was subsequently considered related to study drug will be considered treatment emergent. Other safety parameters will include vital signs, ECGs, clinical laboratory assessments and physical exams.

7.7.1. Adverse Events

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1 or later) and displayed in tables using System Organ Class (SOC) and Preferred Terms (PT). All treatment emergent AEs hereafter will be referred to as AEs in this document.

An overview table of AEs will be tabulated. The overview table will include the number and percentage of patients in following categories such as, 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 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

Tabulations by System Organ Class (SOC) and Preferred Term (PT) displaying the number of patients (percentage) and total events will be produced for the following tables:

- All AEs
- Severe AEs
- AEs by Maximum Severity
- AE related to treatment
- AEs related to treatment by Maximum Severity
- All SAEs
- SAEs related to treatment
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AEs leading to withdrawal

Tabulations by PT in decreasing order in frequency within the lumasiran arm will be generated for the following tables:

- All AEs
- All SAEs
- AEs related to treatment
- SAEs related to treatment

There will also be an All AE table generated displaying rates of adverse events adjusted for exposure-time during the respective period.

AE and SAE tables will be generated for each of the following subgroups: Age, Gender, Race, and eGFR categories.

Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence or most related.

Separate listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug, withdrawal of study drug and/or dose interruption. By-subject AE listings will be provided.

Additional summaries of other Standardised MedDRA Queries (SMQs) or adverse event grouping may be summarized such as but not limited to the following:

> **Injection Site Reactions [ISRs]**: AEs mapping to the High-Level Term (HLT)=" Injection Site Reactions" using MedDRA dictionary will be included in the summary. Frequency (percentages) of ISRs by HLT and PT will be generated. A separate listing will be generated to display all patients who reported ISRs.
>
> A table 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 two consecutive injections, then these events will be considered as 1 ISR and considered related to the earlier injection.
>
> **Hepatic AEs, including AEs of LFT abnormalities**: These AEs are mapped to the Standardized MedDRA Query (SMQ) drug-related hepatic disorders - comprehensive search (includes all narrow and broad terms). Frequency (percentages) of drug-related hepatic disorders will be summarized by SOC and PT. A separate listing will be generated of all patients reporting these events.

7.7.2. Clinical Laboratory Data

Clinical laboratory parameters will be expressed in Standard International (SI) units. Laboratory data collected and recorded below lower limit of quantification (LLQ) will be set to the lower limit of detection for calculation of summary statistics. Summaries will only include data from central laboratory. eGFR will not be reported in this section, as this is summarized in the efficacy section. For any local collections of LFTs, these will be included in a separate data listing. Key laboratory parameters will be graded according to NCI CTCAE v5.0.

Summaries for each lab parameter (hematology, chemistry, liver function tests, coagulation and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics at each scheduled visit. Descriptive statistics include actual value, change from baseline and percent change from baseline at each scheduled visit.

Shift tables will be generated to summarize shifts from baseline categories to the worst post-baseline categories with directionality specified for any labs which could be reported in either direction (e.g. above ULN or below ULN).

Clinical laboratory tests with normal ranges will be classified as Low, Normal, and High. For these tests, abnormal values will be flagged in the listings with H when the value is higher than the upper limit of the reference ranges and with L when the value is lower than the lower limit of the reference ranges.

For hematology and chemistry labs, summary tables of potentially clinically significant abnormalities will also be provided.

All laboratory data will be presented in data listings. Separate listings will be included for those laboratory data collected from local labs such as LFTs. Out of range laboratory results will be identified in listings.

Liver Function Tests (LFTs): A listing will be generated for all patients with abnormal liver function tests as defined by ALT>3xULN, AST>3xULN and total bilirubin >2x ULN at any visit.

A tabular summary for LFTs will be generated to summarize the number and associated percentage of patient in each of the categories at any post-baseline visit:

- ALT>1 & ≤3, ALT>3 & ≤5, ALT>5 & ≤10, ALT>10 & ≤20, ALT>20xULN
- AST>1 & ≤3, AST>3&≤5, AST>5& ≤10, AST>10 & ≤20, AST>20xULN
- ALT or AST>1 & ≤3, ALT or AST>3 & ≤5, ALT or AST>5 & ≤10, ALT or AST>10 & ≤20, AST or ALT>20xULN
- WNL, ALP>1.5xULN
- Total Bilirubin>1.5& ≤2, Total Bilirubin>2&≤3, Total Bilirubin>3& ≤5 and Total Bilirubin>5

eDISH plots of peak total bilirubin at any time versus peak ALT or AST at any time will also be presented.

For selected labs (e.g. ALT/ULN and AST/ULN), a table and figure of the values across the entire study will be generated by treatment sequence arms.

7.7.3. Vital Signs

Descriptive statistics for each vital sign (e.g. systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, weight, body mass index) will be summarized at scheduled visits. Summaries will include actual values and changes from baseline. A summary table of potentially clinically significant shifts in vital signs will also be generated separately for pediatric patients (<18 years old) and adult patients.

For any patient <18 years old at screening, the modified z-score will be calculated for height, weight and body mass index (BMI) according to the CDC growth chart. A summary table of descriptive statistics of z-scores by visits and treatment arm will be summarized. A tabular summary of the proportion of patients with z-scores at various cut-points (e.g. ≥+/- 2 SD) will also be summarized as well.

A separate listing of vital sign data will be generated. Per patient plots of z-scores over time for those patients <18 years old at screening will also be generated.

7.7.4. Physical Examinations

During the study, full physical examinations and abbreviated physical examinations will be conducted throughout the study. If any abnormalities are observed during these physical exams, then this will be recorded on the adverse event form.

A separate listing per patient will be generated to display the date and time of the physical exam.

7.7.5. Electrocardiogram

Electrocardiogram (ECG) parameters include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and QTc interval. Corrected QT interval (QTc), if not collected, will be calculated using the Fridericia's correction formula.

Fridericia's cube-root corrected QT: QTcF (ms) = QT (ms) × $\sqrt[3]{\frac{HR(bpm)}{60}}$.

The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each timepoint will be summarized.

For electrocardiogram parameters, these will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation.

Baseline, post baseline maximum QTcF and post baseline maximum change from baseline in QTcF during the study will be summarized with descriptive statistics. The incidence of notable ECG changes from baseline in maximum absolute QT_cF, intervals (<=450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QT_cF, maximum changes from baseline (<=30 ms, > 30 -60 ms and > 60 ms) over all post-treatment evaluations will be summarized.

A listing of all ECG data will be provided.

7.8. Anti-Drug Antibody

The number and associated percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized by treatment group. A listing of patients with positive ADA assay results will be provided as well as a listing of all ADA results.

8. CHANGES TO PLANNED ANALYSES

Below is a summary of changes in the Statistical Analysis Plan (SAP) version 2.0 which differ from SAP version 1.0 with corresponding rationale of why the change had been made.

Summary of Changes	**Rationale**
List and order of secondary endpoints are modified (Section 3.2 and Section 5.6).	The change to the list of secondary endpoints is made to align with protocol amendment 2. Additionally, additional results from ALN-GO1-001 was evaluated to change the order of secondary endpoints to mitigate the risk
Changes to sensitivity analysis to primary endpoint (Section 7.1): • Replace the initially planned sensitivity analysis with 2 sensitivity analyses to evaluate the assumption of steady state from month 3 to month 6 • Remove per-protocol analysis	The initially planned sensitivity analysis evaluates an endpoint of percent change from baseline at Month 6, which differs from the primary endpoint. Furthermore, this analysis is covered by the newly added sensitivity analysis. New sensitivity analyses are added to evaluate the sensitivity to the estimated treatment effect of the primary analysis by the assumption of lumasiran reaching steady state of the treatment effect at Month 3 and maintained through Month 6. Per-protocol analysis, though it helps address a question related non-compliance, does not provide additional evidence to efficacy.
Secondary endpoint (Section 3.2) Percent change in 24-hour urinary oxalate: creatinine ratio ~~(value/ULN)~~ from baseline to Month 6	The endpoint is modified because the 24h urinary oxalate: creatinine ratio upper limit of normal for ages 6 years and older is being extrapolated from the healthy adult population assessed with the validated PD assay [redacted]. This extrapolation is supported by published data that suggest oxalate: creatinine in children 6 and above is similar to adults.
ULN value for 24-hour urinary oxalate corrected by BSA is defined in Appendix	The ULN for the [redacted] assay has been determined based on 100 samples from healthy normal volunteers. Refer to Biomarker white paper for details. The initial ULN value quoted is ULN for Clinical Diagnostic Assay from [redacted] hence is not applicable and removed.
Plasma Oxalate Analysis Set is added for the analysis of plasma oxalate endpoints	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 at LLOQ are excluded from the analysis to ensure the meaningful reduction can be evaluated for the study population.
Add SAE and AE subgroup analyses for the double blinded period	These safety analysis by Age, Race, Gender, Region, eGFR are aligned with ISS

Summary of Changes	Rationale
Other edits throughout	To improve clarity

9. REFERENCES

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

[redacted]

APPENDIX A. UPPER LIMIT OF NORMAL FOR 24-HOUR URINARY OXALATE CORRECTED FOR BSA

To establish accurate and reproducible reference ranges of oxalate and glycolate levels in urine and plasma of healthy subjects, human urine and plasma samples from healthy male and female subjects were procured from BioIVT (formerly Bioreclamation IVT, Westbury, NY, USA), a commercial provider of biological samples. Of these samples, 24-hour urine samples were available from 100 healthy adults. Samples were processed and analyzed for oxalate using Quantitative PD Assay validated at [redacted].

The ULN, based on these samples, for 24-hour urinary oxalate corrected for BSA is estimated to be 0.514 mmol/24hr/1.73m^2. Details for sample collection and analysis and statistical method for ULN determination will be available from the white paper for Urinary and Plasma Levels in Healthy Subjects.