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STATISTICAL ANALYSIS PLAN

A Phase 2 Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients with Primary Hyperoxaluria Type I

Protocol Number:	ALN-GO1-002
Protocol Version and Date:	Original Protocol, 30 March 2017
Investigational Drug:	Lumasiran (ALN-GO1)
Phase:	Phase 2
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Analysis Plan Version and Date:	Version 1.0, 23 May 2019

Confidentiality Statement

APPROVAL SIGNATURE PAGE

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ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the concentration-time curve
BSA	Body surface area
C_{max}	Maximum plasma concentration
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EQ-5D	Euro Quality of Life Health State Profile Questionnaire
ESRD	End-stage renal disease
GO	Glycolate oxidase
HLT	high level term
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
PD	Pharmacodynamic(s)
PedsQL	Pediatric Quality of Life
PH1	Primary hyperoxaluria type 1
PK	Pharmacokinetic(s)
PT	Preferred term
SAP	Statistical Analysis Plan
SOC	System Organ Class
SRC	Safety Review Committee

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.[1] As renal function declines, elimination of oxalate is further reduced, such that calcium oxalate accumulates in bone, vasculature, skin, retina, heart, and nervous system, resulting in severe end-organ damage. This devastating condition, systemic oxalosis, arises when the estimated glomerular filtration rate (eGFR) has declined below 30 to 45 mL/min/1.73 m^2.

The analysis methods described in the protocol may be updated in this statistical analysis plan (SAP). Any changes to the data analysis methods described in the protocol, including justification for the changes, are described in Section 8 and in 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

Study ALN-GO1-002 is an open-label, extension study designed to evaluate the long-term safety, pharmacokinetic (PK) and pharmacodynamics (PD) of subcutaneously administered lumasiran in patients with PH1 who completed the parent study (ALN-GO1-001). The number of patients may include up to 20 PH1 patients from Part B of Study ALN-GO1-001.

Eligible patients either receive the same dose and/or dose regimens of ALN-GO1 (hereinafter referred to as lumasiran) as administered in the parent study (1.0 mg/kg once monthly, 3.0 mg/kg once monthly or 3.0 mg/kg once every 3 months) or may change dose regimens at any time. Any change in dose regimen for a patient may occur due to emerging data and with the approval from the Safety Review Committee (SRC).

2.2. Study Procedures

The schedule of assessments is described in the study protocol (Table 1 and Table 2).

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

- Evaluate the long-term safety of multiple doses of lumasiran in patients with PH1

3.1.2. Secondary Objectives

- Evaluate the PD effect of lumasiran on urinary oxalate excretion
- Characterize the effect of lumasiran on markers of renal function

3.1.3. Exploratory Objectives

- Characterize the PK of lumasiran
- Evaluate the PD effect of lumasiran on urinary glycolate, plasma oxalate concentration, plasma glycolate concentration and urine oxalate:creatinine ratio
- Characterize the quality of life
- Evaluate the incidence of anti-drug antibodies (ADA)

3.2. Endpoints

3.2.1. Primary Endpoint

- Incidence of adverse events (AEs)

3.2.2. Secondary Endpoints

- Change in urinary oxalate excretion over time
- Change in eGFR and measured creatinine clearance (mCrCl) over time

3.2.3. Exploratory Endpoints

- Describe the effect of lumasiran on other safety parameters, including assessments of vital signs, electrocardiograms (ECG), renal ultrasounds, clinical laboratory parameters, and physical examinations
- Assess lumasiran plasma PK parameters including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life, area under the curve, fraction of dose excreted in urine, apparent clearance and apparent volume of distribution.
- Change from baseline over the course of the study in the following PD parameters: urinary glycolate excretion, plasma oxalate concentration, plasma glycolate concentration and urine oxalate:creatinine ratio
- Quality of life as assessed by Kidney Disease Quality of Life Questionnaire (KDQOL) for adults (≥18 years of age) and the PedsQOL (the generic and ESRD modules) for children (<18 years of age)
- Incidence of ADA

4. PATIENT POPULATION

4.1. Patient Definitions

The populations (analysis sets) are defined as follows:

- Safety Analysis Set: All patients who receive any amount of study drug.
- PD Analysis Set: All patients who receive any amount of study drug and who have at least 1 post-dose urine sample for PD.
- PK Analysis Set: All patients who receive any amount of study drug and who have at least 1 post-dose PK concentration measurement.

The Safety Analysis Set will be used to analyze safety and clinical activity data. The PK and PD Analysis Sets will be used to conduct PK and PD analyses, respectively.

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 study 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.

Protocol deviations will be summarized in the CSR.

5. GENERAL STATISTICAL METHODS

5.1. 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 the database plus 1 additional decimal. The 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 patients <18 years of age), 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 repeated collections at a particular visit then the median will represent the value at that visit. For biomarker and/or laboratory data, if any value is recorded as less than the lower limit of quantification (LLOQ) then the value used for calculations will be assigned a value of 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.

Study Day 1 will be defined as the day of the first dose of lumasiran in this study. Study day will be calculated relative to the 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 the assessment date is before the date of the first dose of study drug, then the study day will be calculated as:

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

5.2. Computing Environment

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

5.3. Baseline Definitions

Baseline will be defined as the derived baseline value in Study ALN-GO1-001 (refer to SAP ALN-GO1-001, Version 2.0; dated August 13, 2018). For data not collected in the parent study (e.g. KDQOL-36, PedsQOL, Renal Ultrasounds), the baseline value will be defined as the latest collection prior to the first dose of lumasiran in this study.

5.4. Dose Groups

All tables and figures will be presented by the initial dose regimens in this study, unless otherwise specified:

- 1 mg/kg once monthly
- 3 mg/kg once every 3 months
- Pooling of 1 mg/kg once monthly or 3 mg/kg once every 3 months
- 3 mg/kg once monthly
- Total

5.5. Missing Data

For continuous and categorical variables, data will not be imputed unless otherwise specified.

For safety analyses, any AEs with fully missing dates or partially missing dates, no date will be assigned. 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.

5.6. Visit Windows

Data will be tabulated and analyzed per the visit as recorded on the electronic case report forms (eCRF) with the exception of visits prior to the first dose in this study [*Note: Protocol states any assessments performed in the parent study within 30 days before the first dose in Study 002 do not need to be recollected (except for vital signs and physical examination)*]. For any data that did not need to be recollected prior to the first dose in this study, the data at the latest visit from the parent study will be used for analysis.

Data at unscheduled visits will be included in by-patient listings and figures, but no assignment to a scheduled visit will be made for the purposes of by-visit summary tabulations. However, unscheduled visits will be considered for any categorical summaries (e.g., shifts from baseline to worst post-baseline value). For patients who discontinue study treatment, the time window for monitoring AEs and collecting PD assessments will be up to 84 days after the last dose.

5.7. Interim Analysis

Interim analyses will be performed to support regulatory activities and publications. These analyses will be descriptive in nature and will not involve any formal hypothesis testing.

For interim analyses, as this study will be ongoing, a cut-off approach will be implemented to ensure data quality. The interim analysis will include data entered on or prior to a pre-specified cutoff date. For assessments with start or end dates (e.g., exposure, AEs, medical history, etc), the start date will be compared to the prespecified cutoff date to determine whether the assessment is included in the analysis.

6. STUDY ANALYSES

6.1. Patient Disposition

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

- Enrolled (signed informed consent and met eligibility)
- Safety Analysis Set
- PD Analysis Set
- PK Analysis Set

Summaries of the number and percentage of patients who discontinued treatment based upon the primary reason for discontinuation (e.g., AE, death, lost to follow-up, etc) will be presented. Summaries of the number and percent of patients who withdrew from the study prematurely and the associated reasons for withdrawal will be presented. Per patient data listings will be presented displaying the primary reason that the patient discontinued treatment and/or went off study.

6.2. Demographics and Baseline characteristics

Baseline characteristics will be based upon the derived baseline in Study ALN-GO1-001 (refer to ALN-GO1-001 SAP; dated August 13, 2018). These characteristics include but are not limited to age, gender, race, ethnicity, body weight, body height as well as baseline 24-hour urinary oxalate excretion corrected for body surface area (BSA), 24-urinary oxalate: creatinine ratio and eGFR. For a subset of baseline parameters (e.g. Quality of Life, renal ultrasounds, etc..), the baseline will be based upon the first dose of lumasiran in this study.

6.3. Medical History

Data recorded in medical history in this study and in the parent study (ALN-GO1-001) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), high level term (HLT) and preferred term (PT). A patient will only contribute once to the count for a given condition (overall, by SOC, by HLT, by PT). Medical history and pregnancy test results will also be presented in data listings.

6.4. Concomitant Medications

Concomitant medications are defined as medications which were taken after the first dose date of the study drug in this study and any medication that started prior to the first dose in this study and was ongoing on or after the date of the first dose of study drug in this study.

Tabular summary of the number and percentage of patients taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and PT. Data will be presented for the Safety Analysis Set. A separate tabular summary of concomitant vitamin B6 use will be summarized by ATC and PT.

By-patient listings will be generated separately for concomitant medications and vitamin B6 medications.

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 doses per patient, cumulative number of doses received per study group, duration of drug exposure (months) per study group, cumulative drug exposure time (months) per study group, 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.

Dose interruptions and compliance are not taken into account.

A separate per-patient exposure listing will be generated to display the initial dosing regimen in the parent study (ALN-GO1-001), the initial dosing regimen in this study and changes to the dose and/or regimen during this study.

7. STATISTICAL ANALYSIS

7.1. Primary Endpoint

7.1.1. Evaluate the incidence of Adverse Events (AEs)

The primary safety parameter is the assessment of treatment-emergent AEs which will be defined as an AE that occurs or worsens on or after the first lumasiran dose date/time of this study though 84 days after the last dose of study drug. In addition, any AE that worsens in intensity or was subsequently considered related to study drug will be considered treatment-emergent. All analyses of AEs will be performed on the Safety Analysis Set.

For summaries of AEs, there will be 3 sets of summaries: all AEs, AEs classified as renal stone events and AEs excluding those classified as renal stone events. A medical review of all AEs will be conducted to identify renal stone events.

AEs will be coded using the MedDRA coding system (version 21.0 or later) and displayed in tables and data listings by SOC and PT. Patients who report multiple occurrences of the same PT will be classified according to the most related or most severe category. Patients with a missing relationship to study drug will be classified as the most related category. Drug related AEs include events considered definitely related or possibly related to study drug by the investigator or events with missing relationship.

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 SOC and PT displaying the number of patients (percentage) and total events will be produced for the following tables:

- All AEs
- Serious AEs
- AEs by maximum severity

- AEs related to treatment
- AEs and SAEs related to treatment by maximum severity

There will also be an all AE table generated displaying rates of AEs adjusted for exposure-time.

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

A subset of key AE outputs will also be generated to compare study groups of patients initially dosed with 3 mg/kg once monthly versus 3 mg/kg once every 3 months of lumasiran. Tabulations of the AE data will be adjusted for exposure-time.

Summaries of other Standardised MedDRA Queries (SMQs) or AE groupings may be summarized such as but not limited to the following:

Injection Site Reactions [ISRs]: AEs mapping to the 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 injections, total number of injections complicated by ISRs and corresponding % of injections complicated by ISR with the most common 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 preceding injection.

Hepatic AEs, including AEs of liver function test (LFT) abnormalities: AEs mapping to the 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.

7.2. Secondary Endpoints

7.2.1. Evaluate the pharmacodynamic effect of lumasiran on urinary oxalate excretion

The analysis of 24-hour urinary oxalate excretion corrected for BSA will be based upon the results that meet the validity criteria (i.e., creatinine excretion ≥10 mg/kg, duration of collection 18 to 26 hours, no missing voids and the sample was not collected within 14 days after the most recent dialysis session, if applicable). The analysis will be generated separately based upon data from laboratories using a clinical diagnostic PD assay or quantitative PD assay.

Correlations between the assays will be performed comparing oxalate values, 24-hour urinary oxalate corrected for BSA, change and percentage change of 24-hour urinary oxalate corrected for BSA. Per-patient spaghetti plots may also be generated to compare the results over time.

24-hour urinary oxalate (mmol/24h/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.

Data will be summarized descriptively at baseline and at each post-baseline visit. Tabular summaries will include actual value, change from baseline and percent change from baseline at each scheduled visit. Per-patient figures and mean (+/-SEM) plots over time of the actual values, change from baseline and percent change from baseline will be generated. A table of the maximum percent reduction per patient will also be generated.

An analysis of the percentage of time at or below 1.5 x ULN will also be summarized. For each patient, the percentage of time will be calculated as follows:

$$\text{Percentage of time at or below 1.5x ULN} = \frac{\text{cumulative months at or below 1.5 x ULN}}{\text{cumulative months of valid assessments}} * 100$$

where cumulative months at or below 1.5x ULN will be defined as the summation across all intervals that met the threshold of at or below 1.5x ULN and cumulative months of valid assessments will be defined as the summation across all valid post-baseline collections. In order to quantify the months at or below 1.5x ULN, a linear interpolation method will be used 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 1.5x ULN (among the subset of patients who had at least 1 post-baseline value that was at or below 1.5x ULN) will be presented. In addition, the number of patients and associated percentage of patients in each category (e.g., <25%, 25 to <50%, 50 to <75%, and ≥75%) will also be presented.

The analysis of the percentage of time will also be calculated using the threshold of at or below ULN.

7.2.2. Change in estimated glomerular filtration rate (eGFR) and measured creatinine clearance over time

Analyses of eGFR and measured creatinine clearance over time will be performed on the Safety Analysis Set.

The eGFR (mL/min/1.73m^2) will be calculated from serum creatinine (SCr) based on the Modification of Diet in Renal Disease (MDRD) formula for patients ≥18 years of age at enrollment and the Schwartz Bedside Formula for subjects <18 years of age at enrollment in the parent study.

MDRD Formula

- eGFR (mL/min/1.73m^2) = $175 \times (S_{Cr}\,[\mu mol/dL]/88.4)^{-1.154} \times (age)^{-0.203} \times$ (0.742, if female), or × (1.212, if African American)

Schwartz Bedside Formula

- eGFR (mL/min/1.73m^2) = (36.2 × height [cm])/ S_{Cr} (µmol /dL)

The eGFR (mL/min/1.73 m^2) will be categorized into the following categories: ≥90, 60 to <90, 30 to <60, 15 to <30, and <15. A shift table of baseline to worst post-baseline eGFR (i.e., category with the lowest value) will be presented. Additionally, the eGFR will also be summarized descriptively at each scheduled visit. The descriptive statistics will include actual value, change from baseline and percent change from baseline at each scheduled visit. Per-patient plots and mean (+/- SEM) plots over time of the actual values, change from baseline and percent change from baseline will be generated. Additionally, slope of change of eGFR over time is will be estimated by a linear mixed effect model, if appropriate.

Analysis of measured creatinine clearance will be performed on the PD Analysis Set. The analysis will include only valid values (note: valid is defined as: creatinine ≥10 mg/kg, duration of collection 18 to 26 hours, no missing voids, and the sample was not collected within 14 days after the most recent dialysis session, if applicable).

Measured urine creatinine clearance at each visit per patient will be calculated as:

> Urine Creatinine concentration (mg/dL)*24-hour urine volume (mL)/ plasma creatinine (mg/dL)*total minutes of collection time*1.73/BSA

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

Tabular summaries will include actual value, change from baseline and percent change from baseline at each scheduled visit.

Per-patient figures and mean (+/-SEM) plots over time of the actual values, change from baseline and percent change from baseline will be generated.

7.3. Exploratory Endpoints

7.3.1. Other Safety Parameters

Additional safety parameters include clinical laboratory parameters (hematology, serum chemistry, LFTs, urinalysis, and coagulations), vital signs, 12-lead ECGs, renal ultrasounds and physical examinations. All additional safety parameters will be analyzed using the Safety Analysis Set.

Clinical Laboratory Parameters: Clinical laboratory parameters will be expressed in SI units. Laboratory data collected and recorded below the LLOQ will be set to the lower limit of quantification for the calculation of summary statistics. Summaries will only include data from the central laboratory (except eGFR as this is summarized in efficacy). Key laboratory parameters will be graded according to NCI CTCAE v5.0.

Laboratory parameters (hematology, chemistry, liver function tests, coagulation and urinalysis), which are continuous variables, will each 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 threshold or below threshold).

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 grade appended (e.g. H1 will represent that the lab reported met the threshold of high range with grade 1).

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

All laboratory data will be presented in data listings. 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 >3 × ULN, AST >3 × ULN or total bilirubin >2 × ULN at any visit.

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

- ALT >1 and ≤3, ALT >3 and ≤5, ALT >5 and ≤10, ALT >10 and ≤20, ALT >20 × ULN
- AST >1 and ≤3, AST >3 and ≤5, AST >5 and ≤10, AST >10 and ≤20, AST >20 × ULN
- ALT or AST >1 and ≤3, ALT or AST >3 and ≤5, ALT or AST >5 and ≤10, ALT or AST >10 and ≤20, AST or ALT >20 × ULN
- WNL, ALP >1.5 × ULN
- Total bilirubin >1.5and ≤2, total bilirubin >2 and ≤3, total bilirubin >3 and ≤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.

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 of age at screening, the modified z-score will be calculated for height, weight and body mass index (BMI) according to the CDC growth chart f. Descriptive statistics of z-scores by visit and treatment arm will be summarized. A tabular summary of the proportion of patients with z-scores at various cut-points (e.g., above and below 2 SD) will also be summarized.

A separate listing of vital sign data will be generated. Per patient plots of z-scores over time for those patients <18 years of age at screening in Study 001 will also be generated.

12-lead ECGs: 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 time point 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 to 60 ms and > 60 ms) over all post-treatment evaluations will be summarized.

A listing of all ECG data will be provided.

Physical Examinations: During the study, full physical examinations and symptom directed physical examinations will be conducted. If any abnormalities are observed during these physical examinations or worsened from baseline, then this will be recorded on the AE form.

A separate listing per patient will be generated to display the dates and times of the physical examination.

Renal Ultrasounds: During the study, renal ultrasounds will be collected at baseline, Month 12 and Month 24. The number and percentage of patients at baseline with findings of normal, abnormal, not clinically significant, clinically significant will be summarized. In addition, the number and percentage of patients in categories to indicate if a significant change from baseline has been documented will also be summarized at each post-baseline visit. Listings will also be generated.

7.3.2. Characterize the Pharmacokinetics of lumasiran

PK analyses will be conducted using noncompartmental methods using data with intensive plasma and urine PK samples. PK parameters will be calculated using a validated version of Phoenix® WinNonlin.

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

7.3.3. Evaluate the Pharmacodynamic Effect of lumasiran

Analysis of PD parameters (e.g. 24-hour urine oxalate: creatinine ratio, plasma oxalate, urinary glycolate concentrations, plasma glycolate concentrations) will be performed on the PD Analysis Set. The analysis will be performed based upon data from clinical diagnostic PD assay and quantitative PD assay. For all 24-hour urine parameters with the exception of 24-hour oxalate:creatinine ratio, only valid values will be used in the analysis (note: valid is defined as: creatinine ≥10 mg/kg, duration of collection 18 to 26 hours, no missing voids and the sample was not collected within 14 days after the most recent dialysis session, if applicable).

Data will be summarized descriptively (n, mean, SD, SEM, median, quartiles, minimum and maximum) at baseline at each post-baseline scheduled visits. Tabular summaries of actual value, change from baseline and percent change from baseline will be generated at each

scheduled visit. Plots of the mean (+/-SEM) of actual values and percent change will also be generated. Per-patient plots of actual values over time will be generated.

For urine oxalate: creatinine ratio and plasma oxalate, the maximum mean reduction from baseline over time will be summarized descriptively.

7.3.4. Characterize Quality of Life (QOL)

Data from the QoL instruments will be collected to assess kidney disease specific measures. Analyses of these instruments will be performed on the Safety Analysis Set. The instrument used is based upon the age of the patient at screening; for each patient, the instrument selected based on age at screening will be used consistently throughout the study. Table 1 outlines the QOL instruments to be used based upon age at screening.

Table 1: QOL Instruments by Age at Screening in Study 002 (<18 years vs ≥18 years)

Age at Screening	QOL Instruments	Domains/Subscales	Notes
≥18 years of age	KDQOL-36	5 subscales: SF-12 Physical Component Score, SF-12 Mental Component Score, Symptoms/Problems, Effects of Kidney Disease and Burden of Kidney Disease	No common variables.
<18 years of age	PedsQL and ESRD model	PedsQOL: 4 multi-dimensional scales: Physical Functioning, Emotional Functioning, Social Functioning and School Functioning 3 summary scores (total score, physical health summary score and psychosocial health summary score). ESRD:7 domains: General Fatigue, About My Kidney Disease, Treatment Problems, Family and Peer Interaction, Worry, Perceived Physical Appearance, and Communication. Total Score	

For each instrument, descriptive statistics will be generated at baseline and each post-baseline scheduled visit. For the PedsQL, both parent and/or child may complete the questionnaire. Summary statistics at each visit for each subscale/score will summarize responses separately based upon the parent and child responses.

7.3.5. Incidence of ADA

The number and associated percentage of patients who are ADA positive at baseline and at any post-baseline visit will be summarized. A listing of patients with ADA positivity with their associated titer value AEs will also be provided.

8. CHANGES TO PLANNED ANALYSES

9. REFERENCES

1. Cochat, P. and G. Rumsby, *Primary hyperoxaluria.* N Engl J Med, 2013. **369**(7): p. 649-58.

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