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STATISTICAL ANALYSIS PLAN

ILLUMINATE-C: A Single Arm Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1)

Protocol Number:	ALN-GO1-005
Protocol Version and Date:	Original Protocol: 16 May 2019 Amendment 1: 06 May 2020
Investigational Drug:	ALN-GO1 (Lumasiran)
Phase:	Phase 3
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Tel: +1 (617) 551-8200 Fax: +1 (617) 551-8101
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Analysis Plan Version and Date:	Original: Version 1.0: 30 January 2020 Amendment 1: Version 2.0: 15 March 2021

Confidentiality Statement

APPROVAL SIGNATURE PAGE

ILLUMINATE-C: An Open-Label Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1

Protocol Number:	ALN-GO1-005
Analysis Plan Version and Date:	Version 2.0: 15 March 2021

This Statistical Analysis Plan has been approved and signed electronically on the final page by the following:

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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
CDC	Center for disease control and prevention
CI	Confidence interval
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulation
CL/F	Apparent clearance
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
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
ESRD	End-stage renal disease
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GO	Glycolate oxidase
ICF	Informed consent form
LFT	Liver function test
LLOD	lower limit of detection

LLN	Lower limit of normal
LOD	Limit of detection
MedDRA	Medical dictionary for regulatory activities
O:C	Oxalate: creatinine
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System Organ Class
SMQ	Standardized MedDRA query
ULN	Upper limit of normal
WHO	World Health Organization
WNL	Within Normal Limits

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 including kidney failure, along with reduced quality of life.[Cochat and Rumsby 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 and Rumsby 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 and Rumsby 2013] Without treatment, the disease progresses inexorably, and death from end-stage renal disease (ESRD) and/or complications of oxalosis can occur.[Cochat and Rumsby 2013; Harambat 2010; van der Hoeven 2012]

The ILLUMINATE-C Study (ALN-GO1-005) is a multicenter, single arm study designed to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of lumasiran in patients with a documented diagnosis of PH1 who have advanced renal disease, as evident by eGFR ≤45 ml/min/1.73 m^2 (or serum creatinine above the upper limit of normal (ULN) for age, in patients <12 months of age). All eligible patients will be administered lumasiran; no control group will be assessed. This statistical analysis plan (SAP) has been developed based on the protocol of the ILLUMINATE-C study (original dated 16 May 2019 and amendment 1 dated 06 May 2020).

The analysis methods described in the protocol may be updated in this SAP. Any change to the data analysis methods described in the protocol, as well as the justification for the change, will be described in the SAP (Section 8) and 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-C study (ALN-GO1-005) is a multicenter, multinational, open-label, single arm Phase 3 study designed to evaluate the efficacy, safety, PK and PD of lumasiran in patients with a documented diagnosis of PH1 who have advanced renal disease, as evident by eGFR ≤45 ml/min/1.73 m^2 (or serum creatinine elevated for age, in patients <12 months of age). All eligible patients will be administered open-label lumasiran; no control group will be assessed. This study will consist of 2 periods: a 6-month Primary Analysis Period followed by a long-term (54 months) extension period.

Lumasiran will be administered as a subcutaneous (SC) injection with weight-based dosing, with dose adjustments for interval weight gain, as follows:

Weight	Loading Dose (Day 1, Month 1, Month 2)	Maintenance Dose (Month 3 and Beyond)
<10 kg	6.0 mg/kg monthly for 3 months	3.0 mg/kg monthly
≥10 to <20 kg	6.0 mg/kg monthly for 3 months	6.0 mg/kg every 3 months
≥20 kg	3.0 mg/kg monthly for 3 months	3.0 mg/kg every 3 months

For patients <6 years of age, the dose will be based on a weight obtained within 7 days prior to dosing. In patients ≥6 years of age, body weight collected within 3 months prior to the study drug dose or the predose weight collected on the study visit day or dosing day will be used for dose calculations.

Patients with weight increases crossing the threshold for the next weight-based dosing category (for example, <10 kg to ≥10 kg or <20 kg to ≥20 kg) will follow the new dosing regimen for the remainder of the study or until the next dosing category threshold is reached (ie, patients will not switch back to the lower-weight dosing schedule if their body weight subsequently decreases).

Patients in maintenance dosing who transition from <10 kg to ≥10 kg will continue to receive monthly doses at 3.0 mg/kg until the next quarterly visit (ie Month 3, Month 6, Month 9, etc.) whereby they will follow every 3-months dosing until the end of the study.

This study will include 2 cohorts. Cohort A will include patients who do not yet require dialysis. Cohort B will include patients who are on hemodialysis therapy. Enrollment to both cohorts will occur concurrently. Cohort A patients who experience progression of renal impairment over time and begin to require long-term dialysis therapy will cross-over to Cohort B. Patients in Cohort A who cross-over to Cohort B prior to their Month 6 visit may be replaced. Patients in Cohort B who stop dialysis during the study will continue in Cohort B.

Patients will be screened from Day -120 to Day -1 to determine eligibility. Consented patients meeting all eligibility criteria will receive their first dose of lumasiran on Day 1. From Screening to Day 1, patients will have at least 4 plasma oxalate collections to establish a robust baseline measurement for plasma oxalate.

As specified in the Schedules of Assessments of ALN-GO1-005 protocol, blood samples will be collected in both cohorts for plasma oxalate sample analysis, to establish plasma oxalate profiles

(AUC) in Cohort B, and for PK parameter analysis in both cohorts. In Cohort B, dialysis status and changes in dialysis regimen will also be monitored and documented. During the first 6 months of the study, changes to the dialysis regimen will not be permitted, except when medically necessary.

Safety assessments will include collection of adverse events (AEs), clinical laboratory tests, vital sign assessments, electrocardiograms (ECGs), physical examinations, and concomitant medications.

2.2. Randomization Methodology

Not applicable

2.3. Blinding

ALN-GO1-005 is an open label study, though pharmacodynamic assessment data will not be distributed to the sites until after the patient has completed the Month 6 visit.

2.4. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will oversee the safety and overall conduct of this study, providing input to the Sponsor. The DMC will operate under the rules of a charter that will be reviewed and approved by the DMC. Details are provided in the DMC Charter.

2.5. Study Procedures

The Schedules of Assessments are described in the study protocol (Tables 1, 2, 3 and 4).

3. ENDPOINTS

3.1. Primary Endpoints

Cohort A

- Percent change in plasma oxalate from baseline to Month 6

Cohort B

- Percent change in pre-dialysis plasma oxalate from baseline to Month 6

3.2. Secondary Endpoints

The following are the secondary endpoints in the Primary Analysis Period:

Primary Analysis Period (Baseline to 6 months)

- Percent change in plasma oxalate AUC between dialysis sessions (Cohort B)
- Absolute change in plasma oxalate
- Change in the following parameters:
  - Urinary oxalate, which is measured by percent and absolute change in 24-hour urinary oxalate excretion corrected for BSA and spot urinary oxalate:creatinine ratio, when available.
  - QoL assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent
- Plasma PK parameters of lumasiran

The following are the secondary endpoints in the Long-term Extension Period:

Long-term Extension Period (6 months to end of study)

- Percent change in plasma oxalate AUC between dialysis sessions (Cohort B)
- Percent and absolute change in plasma oxalate
- Change in the following parameters:
  - Nephrocalcinosis as assessed by renal ultrasound
  - Frequency and mode of dialysis (Cohort B)
  - Frequency of renal stone events
  - Urinary oxalate, measured by 24-hour urinary oxalate excretion corrected for BSA, and spot urinary oxalate:creatinine ratio
  - Renal function as assessed by eGFR (Cohort A)
  - Measures of systemic oxalosis in the following systems:
    - Cardiac

  - Dermatologic
  - Skeletal
  - Ocular
- QoL (quality of life) assessed by the PedsQL Total Score for patients ≥2 to <18 years of age at consent, and as assessed by KDQOL Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales, and SF-12 Physical Component Summary and Mental Component Summary, in patients ≥18 years at consent

3.3. Exploratory Endpoints

The following are the exploratory endpoints:

- Growth parameters in patients who are <6 years of age at consent
- Change in developmental milestones over time in patients <6 years of age at consent
- Change in QoL as assessed by EQ-5D-Y and PedsQL (individual subscales of the generic and ESRD modules, and ESRD module total score) for patients ≥2 to 18 years of age at consent, and as assessed by EQ-5D-5L in patients ≥18 years of age at consent
- Change in QoL as assessed by KDQOL Symptoms and Problems of Kidney Disease subscale in patients ≥18 years of age at consent
- Change in patient and caregiver resource use (eg, work/school attendance, visits to doctor/hospital)
- Change in patient and caregiver experiences as evaluated by a patient experience questionnaire and a caregiver experience questionnaire
- Frequency of ADA
- Change in urinary and plasma glycolate, where urinary glycolate is measured by urinary glycolate:creatinine ratio

3.4. Safety Endpoint

- Frequency of AEs

4. PATIENT POPULATION

4.1. Patient Definitions

The populations (analysis sets) are defined as follows:

- Safety Analysis Set: All patients who received any amount of lumasiran during study.
- Full Analysis Set: All patients who received any amount of lumasiran and have at least one evaluable plasma oxalate value (pre-dialysis in Cohort B) at baseline and at least one evaluable plasma oxalate value from assessment(s) at Month 3 through Month 6
- PK Analysis Set: All patients who received any amount of lumasiran, have at least 1 postdose blood sample for PK parameters, and have evaluable PK data.

The Safety Analysis Set will be used for safety analyses and the sensitivity analysis of efficacy. The Full Analysis Set will be used to evaluate efficacy endpoints. The PK Analysis Sets will be used to conduct PK analyses.

This study will consist of 2 periods: a 6-month Primary Analysis Period followed by a long-term (54 months) extension period. The Primary Analysis Period starts at the first date/time of lumasiran dose administration and ends at either the date/time of lumasiran dose administration at Month 6 (exception being that Month 6 assessments (eg,plasma oxalate and PK assessments) which occur after the Month 6 dose will be included) or the date of the Month 6 visit (Day 169) for patients who discontinued treatment prematurely. Primary analysis will be conducted using the Primary Analysis Period data collected through 6 months.

The Long-term Extension Period, starts at the date/time of lumasiran dose administration at Month 6 and is through the end of the study. Analysis of the Long-term Extension Period will focus on long-term efficacy and safety effects of lumasiran.

Patients who discontinue from study drug during the 6-month Primary Analysis Period (defined above) will be encouraged to remain on the study and complete assessments (including plasma oxalate but excluding PK assessments) through Month 6. They will also be asked to complete safety follow-up visits, once every 3 months, per the safety follow-up schedule for up to 12 months after the last dose of lumasiran.

Patients who discontinue study drug after Month 6 will be asked to return for their next scheduled visit to complete early termination (ET) assessments and complete safety follow-up visits, once every 3 months, per the safety follow-up schedule for up to 12 months after the last dose of lumasiran.

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 an interim or full database lock. All protocol deviations will be presented in a listing.

Major protocol deviations will be summarized in the CSR.

5. GENERAL STATISTICAL METHODS

5.1. Sample Size Justification

The planned enrollment for the study is 20 patients, including at least 6 patients in each cohort.

Of those 20 patients, the planned enrollment includes at least 4 patients <6 years of age at consent, and at least 2 patients between ≥6 to <18 years of age at consent.

The sample size was determined based on feasibility considerations, not power calculations.

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 the database plus one additional decimal. The standard deviation and standard error will be presented to the level of precision collected in the database plus 1 additional decimal. For any assessments with repeated collections at a given study visit (eg height) the mean will represent the value at that visit unless otherwise noted. For biomarker and/or lab data, if any value is recorded as <lower limit of detection (LLOD) then the value assigned for calculations will be the LLOD.

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.

Summaries of tables and figures for each study period will include all data collected during the corresponding period as defined in Section 4.1.

The per-patient listings will include all data collected during each study period. For per-patient listings of the extension periods, there will be a variable to indicate the period of the data collection (Primary Analysis Period or Extension Period).

Day 1 will be defined as the day of the first dose of lumasiran. Study day is calculated relative to the first dose date of lumasiran for all patients:

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

Study Day = Date of assessment – date of first dose of lumasiran + 1,

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

Study Day = Date of assessment – date of first dose of lumasiran

Summary statistics will be presented, as well as 2-sided 95% confidence interval (CI)s for primary/secondary endpoints or 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

In Cohort A patients, the plasma oxalate baseline is defined as the mean of all plasma oxalate level values collected prior to the first dose of lumasiran. In Cohort B patients, the plasma oxalate baseline is similarly defined except that the values obtained from the plasma oxalate profile assessment visits will only include the first pre-dialysis sample collected per visit.

For all patients who are not anuric (anuria is defined as <100 ml of urine per day), single-void urine samples (in triplicate) will be collected during screening, with the mean of values for the various parameters measured in these single-void samples used to establish baseline. In these patients, three 24-hour collections will be performed during Screening, with the median values of all the valid samples used to establish baseline urinary oxalate levels.

A 24-hour urine collection will be considered valid if each of the following criteria are met:

- The collection is between 18 to 26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection.
- In patients not undergoing dialysis, the 24-hour creatinine content is at least 5 mg/kg for patients <6 years of age, and 10 mg/kg for patients ≥6 years of age as measured in the study central laboratory.

In patients undergoing dialysis, 24-hour collections are not required to have a minimum creatinine content to be considered valid.

Urine data collected from patients that are anuric is considered unreliable; thus there will be no analyses performed for patients that were anuric, from whom urine samples are not collected.

In Cohort B, baseline plasma oxalate AUC measurements will be obtained via the plasma oxalate profile assessments prior to the first dose of lumasiran. Plasma oxalate profile assessments will be performed during Screening, with the mean value of all valid AUC profiles (see Section 7.3.1) being computed to establish the baseline AUC.

For other parameters, baseline is defined as the last non-missing value prior to the first dose date/time of lumasiran, unless otherwise specified. The baseline value for any measurements with multiple values at a visit (eg labs, etc.) will be defined as the mean of all values collected on the most recent date of assessment prior to the first dose date/time of lumasiran.

Parameters capturing disease history (eg reported history of renal stone episodes in the past 12 months) at screening will represent the baseline value (adjusted events based on age category will be applied, see Section 10.1).

5.5. Missing Data

Patients who discontinue the study treatment 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 efficacy analysis. However, it is possible that data will remain missing.

Plasma oxalate AUC(0-24h) is considered missing if a plasma sample from any of the four, key collection timepoints (ie, pre-dialysis, 30 minutes before the end of dialysis, 4 hours postdose, and 24 hours post dialysis) is missing. Linear interpolation or extrapolation may be applied to determine the availability of values for these timepoints, if appropriate. For calculation of an AUC for plasma oxalate profile, details are provided in Section 7.3.

For safety analyses, no date will be assigned to any AEs with fully missing dates or partially missing dates. 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 the first dose of lumasiran.

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.

For partial dates of renal stone events (start and stop dates): the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. It is not expected that renal stone dates will be completely missing.

Due to blood sample volume limitations related to patient age/size, missing data in blood sample tests are expected.

The following are considerations for the evaluability of plasma oxalate due to potential post-dose dialysis treatments in Cohort A.

- If a Cohort A patient has at least one plasma oxalate value during Months 3-6 with intervening transient dialysis (<=2 weeks), then the patient's plasma oxalate values that are prior to dialysis and at least 48 hours after the end of the last dialysis session are evaluable and will be included in primary analysis.
- If a patient has at least one plasma oxalate value during Months 3-6 before long-term (>2 weeks) dialysis, then:
  - The patient's plasma oxalate values before the start of dialysis are evaluable and will be included in the primary analysis
  - The patient's plasma oxalate values after the dialysis are unevaluable and will be excluded from the primary analysis
- If a Cohort A patient begins long-term (>2 weeks) dialysis between baseline and Month 3, then the patient's plasma oxalate values post dialysis are unevaluable. Hence, the patient will be excluded from primary analysis for Cohort A and only included in sensitivity analysis

- If a Cohort A patient begins transient (≤2 weeks) dialysis between baseline and Month 3, then:
  - Data collected during the patient's dialysis and recovery period (48 hours) are unevaluable and will be set as missing and be excluded from the primary analysis
  - The remainder of the patient's data including baseline to Month 6 are evaluable and will be used in the primary analysis

The following are considerations for the evaluability of plasma oxalate due to potential dialysis modification (clinically significant change in dialysis prescription as assessed by investigator, e.g., frequency or access modality such as catheter to AV fistula) in Cohort B.

- If a Cohort B patient's dialysis is modified for at least 4 weeks after the Month 3 assessment, plasma oxalate collected before dialysis modification are evaluable and will be included in the primary analysis. Data collected after the dialysis modification will be censored.
- If a Cohort B patient's dialysis is modified for at least 4 weeks prior to the Month 3 assessment, patient data after modification of dialysis are considered unevaluable. Hence, the patient will not be included in primary analysis, but will be included in safety analysis set for the sensitivity analysis.
- If a Cohort B patient's dialysis regimen is modified for less than 4 weeks (from the start of the change to the resumption of the prior dialysis regimen), plasma oxalate values during this modification or within 48 hours following the resumption of the prior dialysis regimen are considered unevaluable and will not be included in the primary analysis.

Data collected after an organ transplant or protocol prohibited treatment may be censored for analysis.

5.6. Visit Windows

For tabular and graphical summaries, 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.

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 if prior to first dosing and for any categorical shift tables (eg shift from baseline to worst post-baseline value).

The following are time windows for the analysis of Plasma Oxalate Profile samples in Cohort B:

Blood Collection Sampling time	Window
Pre-Dialysis	Prior to dialysis on the same day as the dialysis
30 minutes before end of dialysis	from 1 hour prior to end of dialysis through the end of dialysis
30 minutes post-dialysis	after the end of dialysis through 1 hour post-dialysis
2 hours post-dialysis	>1 hour post-dialysis through 3 hours post-dialysis
4 hours post-dialysis	>3 hours post-dialysis through 6 hours post dialysis
8 hours post-dialysis	>6 hours post-dialysis through 10 hours post-dialysis
12 hours post-dialysis	>10 hours post-dialysis through 16 hours post-dialysis
24 hours post-dialysis	>18 hours post-dialysis through pre-dialysis the next day (if dialysis session scheduled day after current dialysis) or 29 hours post-dialysis (if no dialysis session scheduled day after current dialysis)

5.7. Interim Analysis

Potential interim database extractions may be planned for lumasiran regulatory submission purposes and/or publication requests.

5.8. 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 a Primary Analysis Period database lock when the last patient completes all Month 6 visit assessments. All data entered as of the date of the Primary Analysis Period database lock will be included in the summary of the Primary Analysis Period CSR.

After the study is completed (ie all patients complete the Long-term Extension Period and/or required safety follow-up visit(s)), the final database lock will occur, and all data will be summarized in a final CSR.

6. STUDY ANALYSES

6.1. Patient Disposition

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

- Safety Analysis Set
- Full Analysis Set
- PK Analysis Set

Summaries of the number and percentage of patients who discontinued treatment and/or withdrew from the study will be presented, along with the primary reasons for discontinuation of treatment and/or withdrawal from the study. 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 blood sample for plasma oxalate (Cohort A) or pre-dialysis plasma oxalate (Cohort B) for the Month 6 visit.

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

- the patient has completed the end of study (EOS; Month 60) visit, or
- the patient has completed 12 months of monitoring following the final lumasiran dose.

The number and percentage of patients enrolled by country and site will be summarized.

Data listings of those patients who withdrew and/or discontinued treatment including the associated reasons will also be presented. Disposition will be summarized throughout the study. All disposition analyses will be presented by cohort.

6.2. Demographics and Baseline Characteristics

Descriptive statistics of demographic characteristics including but not limited to: age, weight (kg), weight category (0-<10kg, 10-<20kg, ≥20kg), gender, race, ethnicity, region, height (cm), and body mass index (BMI) will be presented. The modified Z-score for patients under age 18 will be calculated and summarized for height, weight and body mass index (BMI) according to the Centers for Disease Control and Prevention (CDC) growth chart.[CDC National Center for Health Statistics 2019]

Additional disease characteristics will be summarized using descriptive statistics. These include but are not limited to: spot urinary oxalate:creatinine ratio (mmol/mmol), plasma oxalate (umol/L), plasma oxalate AUC [umol/L/24hr] (Cohort B only), 24-hour urinary oxalate excretion corrected for BSA (mmol/24hours/1.73m^2), 24-hour urinary oxalate:creatinine ratio (mmol/mmol), eGFR (Cohort A only), spot and 24 hr. urinary glycolate:creatinine ratio (mmol/mmol), plasma glycolate (nmol/L), number of episodes with renal stone events, number of patients reporting pyridoxine (vitamin B6) use at the time of study entry, and presence of systemic oxalosis (Cohort B).

All analyses will be presented by Cohort.

6.3. Medical History

A complete medical and surgical history will be collected at the screening visit. The medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1 or later) and will be summarized for the Safety Analysis Sets.

A tabular summary of historical disease characteristic information will be generated and include information on disease characteristics such as: time from diagnosis to first dose date (months), time from first symptoms to first dose date (months), time from first symptoms to diagnosis (months), number of siblings with PH1, reported history of disease events (eg pyelonephritis, renal stones, kidney stones, urinary tract infection). Reported medical history events may be adjusted based on age category, see Section 10.1.

Separate by-patient listings will be generated.

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 were either ongoing at the time of or stopped before the first dose of the study medication. Concomitant medications are defined as medications which were taken prior to and were ongoing while on lumasiran or medication(s) taken on or after the first dose date of the lumasiran.

A tabular summary of the number and percentage of subjects taking concomitant medications will be generated by anatomic therapeutic class (ATC) and preferred term. Data will be presented for the Safety Analysis Set.

By-patient listings will be generated separately for prior medications, concomitant medications and pyridoxine (vitamin B6). By-patient listings for crystallization inhibitors and erythropoietin (EPO) stimulating agents may also be provided.

7. STATISTICAL ANALYSIS

All endpoints in ALN-GO1-005 will be analyzed by Cohort.

7.1. Primary Endpoint

The primary objective in Cohort A is to evaluate the effect of lumasiran on plasma oxalate in patients who are not on dialysis therapy. The primary objective in Cohort B is to evaluate the effect of lumasiran on pre-dialysis plasma oxalate levels in patients who are on hemodialysis therapy. The primary endpoint is percent change from baseline in plasma oxalate (Cohort A) / pre-dialysis plasma oxalate (Cohort B) to Month 6.

The primary analysis in Cohort A will be performed using a restricted maximum likelihood (REML) based Mixed-effect Model Repeated Measures (MMRM) approach using the FAS. Analysis will include evaluable plasma oxalate values of all scheduled visits through Month 6, which will be modeled with fixed effects of scheduled visits and baseline plasma oxalate, including patient as a random factor. Autoregressive (1) will be used to model the within-patient error given the small sample size for this study. The primary estimate is the least square (LS) mean of the percent change in plasma oxalate from baseline at Month 3 to Month 6, averaged over these timepoints. This LS mean will be presented along with corresponding standard errors (SEMs), 95% confidence intervals (CI) and p-value from the model (ie, testing against the null hypothesis of mean of primary outcome being equal to 0).

If the fit of the autoregressive (1) covariance structure matrix fails to converge, the primary estimate is the LS mean of the primary outcome variable average across scheduled visits from Month 3 to Month 6, according to analysis of covariance (ANCOVA) model with covariate of baseline plasma oxalate. This LS mean will be presented along with corresponding SEMs, 95% CI and p-value from the model.

The primary analysis in Cohort B will be performed using a REML based MMRM approach using FAS. Analysis will include evaluable pre-dialysis plasma oxalate values of all scheduled visits through Month 6, which will be modeled with fixed effects of scheduled visits and pre-dialysis baseline plasma oxalate, including patient as a random factor. Autoregressive (1) will be used to model the within-patient error given the small sample size for this study. The primary estimate is the LS mean of the percent change in plasma oxalate from baseline at Month 3 to Month 6, averaged over these timepoints. This LS mean will be presented along with corresponding standard errors (SEMs), 95% confidence intervals (CI) and p-value from the model (ie, testing against the null hypothesis of mean of primary outcome being equal to 0).

If the fit of the autoregressive (1) covariance structure matrix fails to converge, the primary estimate is the LS mean of the primary outcome variable average across scheduled visits from Month 3 to Month 6, according to the ANCOVA model with covariate of pre-dialysis baseline plasma oxalate. This LS mean will be presented along with corresponding SEMs, 95% CI and p-value from the model.

For each cohort, descriptive statistics and LS mean will also be generated at each scheduled visit. Mean (+/- SEM) figures of percent reduction will be plotted as well as individual spaghetti plots. A table of the mean maximum percent reduction during the 6-months will also be generated. The forgoing analyses will be performed using data from Primary Analysis Period of each cohort.

7.1.1. Sensitivity Analysis

Sensitivity analyses include:

- Percent change from baseline in plasma oxalate (Cohort A) or pre-dialysis plasma oxalate (Cohort B) values to Month 6 by cohorts in Safety Analysis Sets

The sensitivity analyses performed will be similar to that described for the primary analysis above but conducted using the Safety Analysis Set, of which the MMRM models include those patients who have no plasma oxalate assessment Month 3 or beyond.

7.2. Subgroup Analysis

Subgroup analyses will include analyses of primary endpoints by age groups and weight-based dosing groups defined according to the baseline values:

Age group: <2 years, 2 to <6 years, 6 to <18years, ≥18 years

Weight-based dosing category: <10 kg, 10 to <20 kg, and ≥20 kg.

Other subgroups (eg, eGFR for Cohort A) may be examined, if deemed appropriate. Some subgroups (eg, age) may be collapsed due to the small number of subjects in each category.

Subgroup descriptive statistical analysis (N, mean, standard error, median, min, max) will be conducted for primary analysis of percent change from baseline in plasma oxalate (Cohort A) / pre-dialysis plasma oxalate (Cohort B) summarized through Month 6 in Full Analysis Set.

The subgroup analyses may be performed for secondary endpoints in Section 7.3.

7.3. Secondary Endpoints

For secondary efficacy endpoints, Full Analysis Set will be used; for secondary PK endpoints, the PK Analysis Set will be used.

All secondary efficacy endpoints will be analyzed and reported with by-patient listings and by-patient figures of actual values, change from baseline and percent change (where appropriate per endpoint) at each visit. Tabular summaries using descriptive statistics (N, mean, standard error, median, min, max) will be reported. For binary endpoints, the number and percentages of patients in each category will be displayed at each visit. Other analyses may be generated if applicable.

7.3.1. Percent Change from Baseline to Month 6 in Plasma Oxalate AUC between Dialysis Sessions

The objective of the AUC analysis in Cohort B is to evaluate the effect of lumasiran on the change from baseline in plasma oxalate AUC for a patient between dialysis sessions. The plasma oxalate profile assessment consists of an overnight visit requiring collection of up to 8 blood samples for plasma oxalate over the course of a 24-hour span. The plasma oxalate AUC will be measured during screening to establish baseline, Month 3, and Month 6 in the Primary Analysis Period, and at Month 12, Month 36, and Month 48 during the Long-term Extension Period.

For patients in Cohort B, a secondary endpoint of percent change from baseline in plasma oxalate AUC(0-24h) will be summarized at Month 6. Plasma oxalate AUC(0-24h) is defined as

the plasma oxalate area under the curve of the 24 hour window after the pre-dialysis assessment. The AUC(0-24h) plasma oxalate assessment for a patient visit will be considered valid only if both of the following criteria are met:

- Results are available from at least the four key sampling collection timepoints (specifically, pre-dialysis (t = 0), 30 minutes before the end of dialysis (t ~ 4 hr), 4 hours postdose (t ~ 8 hr), and 24 hours post dialysis (t ~ 24 hr);
- The number of days since last dialysis session for a given post-baseline profile is the same as the number of days since last dialysis session during the screening period.

AUC(0-24h) will be calculated using plasma oxalate results with the linear-trapezoidal method using actual collection times relative to pre-dialysis sampling time. An exact 24h assessment for the purpose of calculating the AUC(0-24h) will be calculated using linear interpolation or extrapolation on the two non-missing scheduled assessments closest to the 24-hour timepoint.

Plasma oxalate profiles will be compared across visits within patients. LS mean percent change from baseline plasma oxalate AUC(0-24h) at Month 6 and its associated 95% confidence interval will be estimated using MMRM model including data evaluated at Month 3 and Month 6. Additionally, the AUC(0-24h) parameter will be listed and descriptively summarized by study visit. The Full Analysis Set will be used for this analysis. A similar approach as used for the primary analysis will apply, in case when the model fails to converge.

Additionally, AUC(4-24h) will be similarly analyzed. AUC(4-24h) is defined as the plasma oxalate area under the curve of the 20 hour window from the end of dialysis (30 minutes before the end of dialysis assessment) until the next dialysis session (24h timepoint). This approach is intended to reduce the variability introduced by different dialysis parameters between patients. The percent change from baseline in plasma oxalate AUC(4-24h) will be summarized through Month 6 in a similar manner to the percent change from baseline in plasma oxalate AUC(0-24h) as a sensitivity analysis to the secondary endpoint. The pre-dialysis scheduled assessment will not be required for a valid AUC or utilized in this assessment, otherwise this analysis will remain consistent with methodology to assess the percent change from baseline in plasma oxalate AUC(0-24h).

7.3.2. Change from baseline to Month 6 in other Plasma and Urinary Oxalate Parameters

The analyses for the following secondary endpoints will also be performed using a restricted maximum likelihood based Mixed-effect Model Repeated Measures approach.

- Absolute change from baseline to Month 6 in plasma oxalate during the Primary Analysis Period
- Percent change and absolute change from baseline to Month 6 in 24-hr urinary oxalate corrected for BSA during the Primary Analysis Period
- Percent change and absolute change in spot urinary oxalate: creatinine ratio during the Primary Analysis Period

Analysis by cohort will include evaluable assessments through Month 6, which will be modeled with fixed effects of scheduled visits and baseline covariate of corresponding assessment,

including patient as a random factor. LS mean of an endpoint of Month 3 to Month 6, averaged over these timepoints will be presented along with corresponding SEMs and 95% CIs. The autoregressive (1) covariance structure matrix will be used to model the within-patient error given the small sample size for this study. Similar approach as used for the primary analysis will apply, in case when the model fails to converge.

7.3.3. Quality of Life (QoL)

The KDQOL-36 Burden of Kidney Disease and Effect of Kidney Disease on Daily Life subscales will be collected for adult patients to assess kidney disease specific measures and PedsQL Total score 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. Additionally, SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) will be summarized for patients aged 18 or above.

CBI [redacted]

CBI

[redacted]

CBI [redacted]

7.3.5. Pharmacokinetics

Please see Section 7.5 for Pharmacokinetic analysis plan.

7.4. Exploratory Efficacy Analysis

Efficacy exploratory endpoints will be analyzed using the Full Analysis Set during the Primary Analysis Period and the Long-term Extension Period unless otherwise noted.

Exploratory endpoints will be analyzed and reported with by-patient listings and by-patient figures of actual values, change from baseline and percent change (where appropriate per endpoint) at each visit (scheduled and unscheduled visits). Tabular summaries using descriptive statistics (mean, standard error, median, min, max) will be reported. For binary endpoints, the number and percentages of patients in each category will be displayed at each visit.

7.4.1. Change from Baseline in Cardiac Systemic Oxalosis at Month 6

The change from baseline in Cardiac systemic oxalosis at Month 6 will be assessed by tabulating the number of patients with abnormal LVEF, GLS, or E/e' at baseline who improve by 5% in LVEF, 2% in GLS, and/or 2% in E/e' respectively in at least one of these measures at Month 6 and by assessing the mean change from baseline in these individual measures at Month 6 for all patients in FAS.

7.4.2. Growth Parameters (z-scores) and Change in Developmental Milestones

Change in growth parameters (z-scores) from baseline over time and changes in developmental milestones over time will be summarized descriptively.

The achievement of developmental milestones over time is assessed using Vineland Adaptive Behavior Scales for each scheduled visit for patients <6 years of age at consent. Composite scores for developmental milestones are collected and summarized using Vineland Adaptive Behavior Scales, second version (Vineland-II). Vineland-II consists of 5 domains each with subdomains. The adaptive levels associated with the domain and subdomain composite scores will be categorized and shift tables will be generated, details in Section 10.2. Vineland-II scores of each domain, subdomain, and the adaptive levels will also be presented in by-patient listing.

7.4.3. Quality of Life (QoL)

The change in QoL as assessed by EQ-5D-Y and PedsQL (individual subscales of the generic and ESRD modules, and ESRD module total score) for patients ≥2 to <18 years of age at consent. The change in QoL as assessed by EQ-5D-5L and KDQoL Symptoms and Problems of Kidney Disease subscale in patients ≥18 years of age at consent.

Descriptive statistics for the actual and change from baseline will be presented for each scheduled visit.

7.4.4. Patient and Caregiver Resource Use

The patient caregiver resource use (eg, work/school attendance, visits to doctor/hospital) will be summarized descriptively for each scheduled visit.

7.4.5. Patient and Caregiver Experience

The patient caregiver experience will be summarized descriptively for each scheduled visit.

7.4.6. Anti-drug Antibody

Analysis of ADA is included in Section 7.7.

7.4.7. Percent and Absolute Change from Baseline in Urinary and Plasma Glycolate

The percent and absolute change from baseline in plasma glycolate and spot urinary glycolate: creatinine ratio will each be summarized at each scheduled assessment.

7.5. Pharmacokinetic Analysis

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

7.6. Safety Analyses

Primary safety analysis is a descriptive summary of frequency of AEs using the Safety Analysis Set. Other safety parameters will include vital signs, ECGs, clinical laboratory assessments and physical exams.

Safety analysis will be conducted for the Primary Analysis Period and extension period.

7.6.1. Adverse Events

The primary safety parameter is treatment emergent AEs. A treatment emergent AE will be defined as an AE that occurs or worsens on/after the first dose date/time of lumasiran through 84 days after the last dose. In addition, any AE that worsened in intensity or was subsequently considered related to lumasiran will be considered treatment emergent.

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 generated. The overview table will include the number and percentage of patients in 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
- At least 1 AE leading to treatment interruption
  - At least 1 drug related AE leading to treatment interruption
- 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
- AEs 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 study withdrawal

Tabulations by PT in decreasing order of frequency 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 AEs adjusted for exposure-time.

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-patient AE listings will be provided.

Additional summaries will also be generated:

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. In addition, a table of the number of patients with at least 1 ISR, total number of doses (any dose split into multiple injections will be considered 1 dose), total number of doses with ISRs and corresponding % of injections with ISR with the most common signs and symptoms reported due to ISRs will be generated.

Hepatic AEs, including Liver Function Test (LFT) abnormalities: Analysis of hepatic AEs will include AEs mapping 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.

7.6.2. Dosing and Extent of Exposure

Summaries of exposure will include the following characteristics such as, but not limited to: the total number of doses received per patient, mean number of doses 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, whichever occurs first. The exposure during the Primary Analysis 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.

7.6.3. Clinical Laboratory Data

Clinical laboratory parameters will be expressed in Standard International (SI) units. Laboratory data collected and recorded as below the lower limit of detection (LLOD) will be set to the LLOD for calculation of summary statistics. Summaries will only include data from central laboratory. 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 or later.

Summaries for each lab parameter (hematology, chemistry, liver function tests, and urinalysis) that 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 category to the worst post-baseline category with directionality specified (eg hyper and hypo), including eGFR when applicable.

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 may 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.

LFTs: A listing will be generated for all patients with abnormal liver function tests as defined by alanine aminotransferase (ALT)>3xULN, aspartate aminotransferase (AST)>3xULN or total bilirubin >2x ULN at any visit, where age specific ULN (when applicable) may be used.

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:

- Within normal limit (WNL), 1<ALT≤3, 3<ALT≤5, 5<ALT≤10, 10<ALT≤20, ALT>20xULN
- WNL, 1<AST≤3, 3<AST≤5, 5<AST≤10, 10<AST≤20, AST>20xULN
- WNL, 1<ALT or AST≤3, 3<ALT or AST≤5, 5<ALT or AST≤10, 10<ALT or AST≤20, AST or ALT>20xULN
- WNL, ALP>1.5xULN
- WNL, 1.5<Total Bilirubin ≤2, 2<Total Bilirubin≤3, 3<Total Bilirubin≤5 and Total Bilirubin>5x ULN

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

For selected labs (eg ALT/ULN and AST/ULN), a table and figure of the values across the entire study will be generated.

7.6.4. Vital Signs

Descriptive statistics for each vital sign (eg 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 be generated.

For any patient < 18 years old at screening, a summary table of descriptive statistics of modified z-scores of patient height, weight, and BMI by visits will be generated. A tabular summary of the proportion of patients with z-scores at various cut-points (ie ≥ ±2 SD) will also be generated.

A by-patient listing of vital sign data will be generated. Per patient plots of z-scores over time may also be generated.

7.6.5. Physical Examinations

Full physical examinations and symptom-directed physical examinations will be conducted throughout the study. Clinical significant abnormalities observed during the physical

examination are recorded on the medical history or AE eCRF as appropriate. A separate listing per patient will be generated to display the date and time of the physical exam.

7.6.6. 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) $\times \sqrt[3]{\frac{HR(bpm)}{60}}$.

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 QTcF, intervals (≤ 450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF, 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.

7.7. Anti-Drug Antibody

The number and associated percentage of patients who have confirmed ADA positive results at baseline and/or any post-baseline visit will be summarized. A listing of patients with ADA positivity with their AEs will be provided.

A listing of all ADA data with associated titers will be provided.

7.8. COVID-19 Pandemic Impact Analyses

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

7.8.1. General Impact

Patients who discontinue treatment or stop study participation due to the COVID-19 pandemic will be included in patient disposition summaries. Impact on study participation due to the COVID-19 pandemic, including visit completion, visit location changes, and study drug dosing

and location changes, will be summarized overall on the patient level, and overall and by visit on the event level.

7.8.2. Impact on Efficacy

The final analyses will include COVID-19 pandemic impacted efficacy analyses. These analyses will evaluate the impact of changes in the visit windows for the efficacy assessments made in protocol amendment 1 (dated 06 May 2020) due to the COVID-19 pandemic. Missing efficacy data due to the COVID-19 pandemic will be summarized.

For the primary analysis, the primary and secondary endpoints missed or assessed out of the original protocol window will be noted in the efficacy subject listing.

7.8.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will include the number and percentage of patients, as well as events and event rates, with any AE, any AE related to study drug, any severe AE, any severe AE related to study drug, any SAE, any SAE related to study drug, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study withdrawal, any study drug related AE leading the study withdrawal, and any deaths. AEs mapping to the COVID-19 custom query will be summarized by high level term and preferred term. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified time points. For patients reporting an AE mapped to the COVID-19 custom query, prior medications and concomitant medications will also be presented in separate data listings.

An overall summary of AEs by COVID-19 pandemic phase (ie, pre-, during, post) will include the number and percentage of patients, as well as events and event rates, with any AE and any SAE. Events will be considered during the COVID-19 pandemic if the event occurs on or after the first confirmed case of COVID-19 based on the country where the study site is located, described in Section 10.3.

7.8.4. Other Impacts

Treatment duration may also be summarized by pandemic phase. Protocol deviation due to COVID-19 pandemic will be summarized and will be indicated in the listing of protocol deviations.

8. CHANGES TO PLANNED ANALYSES

Summary of Changes	Rationale
The PK analysis set definition was updated.	The definition in the protocol was updated in the Protocol Amendment 1 dated 06May2020
The Sample Size was modified.	The sample size in the protocol was changed in the Protocol Amendment 1 dated 06May2020
Changes were made in sections 5.5, 5.6, and 7.3.1 to clarify the analyses related to plasma oxalate AUC.	Provided additional details for plasma oxalate AUC related definitions, derivations, and analyses.
Subsections in 7.3 and 7.4 were provided for various endpoints including secondary endpoint analyses during the extension period, exploratory efficacy analyses for the quality of life and patient and caregiver resource use endpoints.	This modification was made to improve readability.
Cardiac Systemic Oxalosis at Month 6 was added to the exploratory endpoints.	To specify the analysis for the primary analysis period.
A section was added for the COVID-19 Pandemic Analyses.	The COVID-19 pandemic occurred after the original SAP.
The COVID-19 Pandemic Phase Start Dates by Country was added to the appendix.	This information was not in the original SAP.
Various editorial changes were made.	To improve clarity

9. REFERENCES

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10. APPENDICES

10.1. Medical History Adjustment

Baseline disease history within the preceding year is required at enrollment. For infants less than one year old, reported values may need to be adjusted to represent a medically meaningful baseline value. Below is an example of the adjustment criteria to be used in such situations, for the outcome of renal stone events:

1. Patients less than 6 months old, baseline records will be presented in by-patient listings, however will not be used in summary tables
2. Patients (≥0.5 and <1 year old): Annualized rate will be calculated from reported data ie if a patient of 8 months old has had 2 renal stone events prior to screening, his/her renal stone event rate at baseline will be 2*(8/12) = 3 events per year
3. Patients (≥1 year old): records at screening for the preceding year will be used to calculate baseline annual stone event rate without adjustment

10.2. Category of Vineland Adaptive Behavior Scale

Vineland adaptive behavior composite scores are collected and summarized using Vineland-II.

The adaptive level of the composite scores can be categorized from "Low" to "High" in the table below.

Adaptive Level of Vineland Composite Scores

Adaptive Level	v-Scale	Standard Score
Low	1 to 9	20 to 70
Moderately Low	10 to 12	71 to 85
Adequate	13 to 17	86 to 114
Moderately High	18 to 20	115 to 129
High	21 to 24	130 to 160

10.3. COVID-19 Pandemic Phase Start Dates by Country

These dates are as reported by the World Health Organization.

Country	Date of 1st Confirmed Case
Australia	26JAN2020
Belgium	04FEB2020
France	24JAN2020
Germany	28JAN2020
Israel	27FEB2020

Jordan	02MAR2020
Lebanon	21FEB2020
Netherlands	28FEB2020
Switzerland	24FEB2020
Turkey	11MAR2020
United Arab Emirates	01FEB2020
United Kingdom	01FEB2020
United States	20JAN2020