Official Title:	**A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients With Primary Hyperoxaluria Type 1**
NCT Number:	**NCT03350451**
Document Date:	**Clinical Study Protocol, 04 May 2020**

CLINICAL STUDY PROTOCOL

ALN-GO1-002

Protocol Title:	A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients with Primary Hyperoxaluria Type 1
Investigational Drug:	lumasiran (ALN-GO1)
EudraCT Number:	2016-003134-24
Protocol Date:	Original protocol, 30 March 2017 Protocol Amendment 1, 27 August 2019 Protocol Amendment 2, 04 May 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor Contact:	PPD , Clinical Research

SPONSOR PROTOCOL APPROVAL

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

PPD

PPD Clinical Development

PPD

Date

INVESTIGATOR'S AGREEMENT

I have read the ALN-GO1-002 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients with Primary Hyperoxaluria Type 1

Product Name

lumasiran (ALN-GO1)

Indication

Primary Hyperoxaluria Type 1 (PH1)

Phase

2

Study center(s)

Up to 15 clinical study centers, worldwide

Objectives

Primary

- Evaluate the long-term safety of multiple doses of ALN-GO1 in patients with PH1

Secondary

- Evaluate the pharmacodynamic (PD) effect of ALN-GO1 on urinary oxalate excretion
- Characterize the effect of ALN-GO1 on markers of renal function

Exploratory Objectives

- Characterize the pharmacokinetics (PK) of ALN-GO1
- Evaluate the PD effect of ALN-GO1 on urinary glycolate excretion, plasma oxalate concentration, plasma glycolate concentration, and urine oxalate:creatinine ratio
- Evaluate the incidence of anti-drug antibodies (ADA)

Endpoints

Primary

- Incidence of adverse events (AEs)

Secondary

- Change in 24-hour urinary oxalate corrected for body surface area (BSA) over time
- Change in 24-hour urinary oxalate:creatinine ratio over time
- Change in estimated glomerular filtration rate (eGFR) over time

Exploratory

- Describe the effects of ALN-GO1 on other safety parameters, including assessments of vital signs, electrocardiograms (ECGs), renal ultrasounds, clinical laboratory parameters, and physical examinations
- Assess ALN-GO1 plasma PK parameters including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), fraction of drug excreted in urine (Fe), apparent clearance (CL/F), and apparent volume of distribution (V/F)
- Change from Baseline over the course of the study in the following PD parameters:
  - Urinary glycolate excretion
  - Plasma oxalate concentration
  - Plasma glycolate concentration
  - Spot urinary oxalate:creatinine ratio
- Incidence of ADA

Study Design

This is a multicenter, open-label, extension study to evaluate the long-term safety, PK, and PD of subcutaneously administered ALN-GO1 in patients with PH1 who completed Study ALN-GO1-001.

Consented eligible patients will enroll in this study and initially receive subcutaneous (SC) injections of ALN-GO1 at the same dose and regimen as they received in Study ALN-GO1-001. Based on emerging data, the safety review committee (SRC) may authorize an alteration of dose and/or dose regimen to one that is no higher than the highest dose evaluated in either Part A or Part B of Study ALN-GO1-001. If such an authorization occurs, dose and/or dose regimen alteration may occur for an individual patient or entire cohort. This alteration may apply to subsequent doses for patients already enrolled and previously dosed in the study and/or to the initial dose and regimen for patients who have not yet been dosed in this study. Patients will be assessed for safety at each study visit. PD assessments will be completed quarterly over the first 12 months on study, and approximately every 6 months thereafter for the study duration. PK assessments will be conducted during the first 12 months of the study.

Patients may receive ALN-GO1 as long as they do not fulfill any of the study discontinuation criteria or until ALN-GO1 is commercially available in the patient's territory or the ALN-GO1 development program is discontinued (whichever comes first).

Number of Planned Patients

Up to 20 patients are planned for enrollment in this study.

Diagnosis and Main Eligibility Criteria

Patients diagnosed with PH1, who completed Study ALN-GO1-001.

Investigational Product, Dose and Mode of Administration

ALN-GO1 will be supplied as a sterile solution in water for subcutaneous (SC) injection. ALN-GO1 is a synthetic, double-stranded small interfering RNA (siRNA) oligonucleotide directed against hydroxyacid oxidase 1 (*HAO1*) mRNA that is covalently linked to a ligand containing 3 *N*-acetylgalactosamine (GalNAc) residues. Patients will initially receive SC injections of ALN-GO1 at the same dose and regimen they received in Study ALN-GO1-001. Based on emerging data, the SRC can authorize an alteration of dose and/or dose regimen to one that is no higher than the highest dose evaluated in either Part A or Part B of Study ALN-GO1-001. If such an authorization occurs, dose and/or dose regimen alteration may occur for an individual patient or entire cohort. This alteration may apply to subsequent doses for patients already enrolled and previously dosed in the study and/or to the initial dose and regimen for patients who have not yet been dosed in this study.

Reference Therapy, Dose and Mode of Administration

Not applicable

Duration of Treatment

The estimated duration of treatment in this study is up to 54 months.

Statistical Methods

Sample size is not determined through a power calculation but based on the anticipated number of patients who complete Study ALN-GO1-001 and are eligible to enroll in this study.

The safety analysis set will include all patients who received at least 1 dose of study drug. Patients with missing PD or PK data will be excluded from those analyses as appropriate.

Incidence of AEs will be summarized by maximum severity and relationship to ALN-GO1. Incidence of serious adverse events (SAEs) and AEs leading to discontinuation will also be tabulated. By-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation.

Descriptive statistics will be provided for clinical laboratory evaluations and vital signs data. Laboratory shift tables from baseline to worst values will be presented. Abnormal physical examination findings, ECG, and echo data will be presented in by-patient listings. Descriptive statistics will be provided for ECG interval data and presented as both actual values and changes from baseline relative to each on study evaluation and to the last evaluation on-study.

Descriptive statistics (eg, mean and standard error of the mean) for observed levels of PD parameters and the relative change from baseline will be presented for each of the postdose follow-up time points.

PK analyses will be conducted using non-compartmental methods. PK parameters including C_{max}, t_{max}, $t_{½\beta}$, AUC, Fe, CL/F, and V/F will be estimated. Other PK parameters may be calculated, if deemed necessary. Anti-drug antibody results will be summarized descriptively. A by-patient listing will also be provided.

Table 1: Schedule of Assessments

Study Stage	**Screen-ing**	**Dosing Period**															**Safety F/U for treatment disc[b]**
Study Visit (Month)	**Screen-ing[a]**	**Base-line[a]**		**For monthly dosing only**		**M3**		**M6**		**M9**		**M12**		**M18 and Q6M after**	**M51 (EOT)**	**M54 (EOS/ET)**	**Every 3 months**
				M1	**M2**												
Study Day	**-30 to -1**	**-1**	**1**	**29**	**57**	**84**	**85**	**168**	**169**	**252**	**253**	**336**	**337**	**Q168D**	**1428**	**1512**	**Q84D**
Visit Window (D)		-7		±7	±7		±7		±7		±7		±7	±28	±28	±28	±28
Informed consent/assent	X																
Demography[c]	X																
Medical history[d]	X	X															
Inclusion/exclusion criteria	X		X														
Full physical examination		X											X			X	
Symptom-directed physical examination				X	X		X		X		X			X			X
Height[e]		X		X	X		X		X		X		X	X		X	X
Body weight and BMI		X		X	X		X		X		X		X	X		X	X
Vital signs[f]			X	X	X		X		X		X		X	X		X	X
12-lead ECG[g]			X				X		X		X		X	X (M24, 36, 48 only)		X	
Echo		X[h]							X				X				
Pregnancy test[i]			X	X	X		X		X		X		X	X	X	X	X
Clinical laboratory assessments[j]			X	X	X		X		X		X		X	X		X	X

Study Stage	**Screening**	**Dosing Period**														**Safety F/U for treatment disc[b]**
Study Visit (Month)	**Screening[a]**	**Baseline[a]**		**For monthly dosing only** **M1**	**M2**	**M3**		**M6**		**M9**		**M12**		**M18 and Q6M after**	**M51 (EOT)**	**M54 (EOS/ET)**	**Every 3 months**
Study Day	**-30 to -1**	**-1**	**1**	**29**	**57**	**84**	**85**	**168**	**169**	**252**	**253**	**336**	**337**	**Q168D**	**1428**	**1512**	**Q84D**
Visit Window (D)		-7		±7	±7		±7		±7		±7		±7	±28	±28	±28	±28
Study drug administration[k]			X (monthly or quarterly) →														
Blood and 24-h urine samples for PK analyses[l]			X						X				X				
Blood sample for PD analyses[m]			X						X				X	X		X	X
24-h urine collection for PD analyses[n]		X				X		X		X		X		X		X	X
Spot urine sample for PD analysis			X	X	X		X		X		X		X	X		X	X
Blood and urine samples for biomarker analyses			X	X	X		X		X		X		X	X		X	
Blood samples for ADA analysis			X						X				X	X		X	X
QOL[o]		X							X				X				
Renal ultrasound[p]		X											X	X (M24, 36, 48 only)		X	
Review/record AEs[q]		X															
Prior and concomitant medications		X															

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; BMI=body mass index; D=day; disc=discontinuation; ECG=electrocardiogram; Echo=echocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; ET=early termination; F/U=follow-up; KDQOL=Kidney Disease Quality of Life Questionnaire; M=month; PD=pharmacodynamics; PedsQL=Pediatric Quality of Life Inventory; PK=pharmacokinetic; Q=every; QOL=quality of life; SC=subcutaneous.

Notes:

- Body weight must be obtained within 4 months prior to dosing.
- Where feasible, when scheduled at the same time points, the assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations, blood sample collections, and urine collections.
- Assessments should be performed predose, where applicable, and unless otherwise noted.
- Grey shaded solid columns indicate the study day when the 24-hour urine collection for PD analysis should begin. Patients may be admitted to the clinical study center to complete the 24-hour urine collections. Assessments may be performed at the study center or at an offsite location (eg, patient's home).
- Visits and study drug dosing may be conducted offsite where applicable country and local regulations and infrastructure allow (at the discretion of the Investigator, based on safety and tolerability) provided the patient has tolerated ALN-GO1 administered in the clinic. If a visit is conducted offsite, a body system assessment may be performed in lieu of a physical examination.
- In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications and adverse events.
- Hatched columns indicate study visits to be conducted **only** for subjects who require monthly dosing.

[a] Screening and Baseline visits may be combined, if possible. Assessments required prior to dosing during the screening or baseline visit in this protocol do not need to be repeated if performed in the ALN-GO1-001 protocol within the 30 days before the first dose with the exception of vital signs, ECGs, and physical examinations.

[b] Patients who discontinue study drug early will be asked to return for their next scheduled visit to complete ET assessments and to complete safety follow-up visits once every 3 months, per the safety follow-up schedule in this table, for up to 6 months after the last dose of lumasiran (Section 5.3.1).

[c] Demographic data will be obtained from Study ALN-GO1-001.

[d] Complete medical history will be obtained at screening and any changes will be updated on admission at the Baseline visit, if different from the Screening visit. Events occurring after signing of the informed consent or assent (if applicable) form and before study drug administration will be captured as medical history.

[e] During the Baseline visit and at EOT, height will be measured in triplicate for all patients; for all other study visits height will only be measured for patients <18 years of age. For patients <18 years of age, at each time point, height will be measured in centimeters, and in triplicate, to facilitate calculation of eGFR using the Schwartz Bedside formula.

[f] Vital signs (blood pressure, heart rate, body temperature, and respiratory rate) will be measured in the supine or seated position after the patient has rested comfortably for approximately 10 minutes. Body temperature can be measured using oral, tympanic, or axillary methods; the temperature measurement method should be consistently utilized for the study duration, if feasible. At Baseline only, vital signs will be measured within 1 hour predose; and 30 minutes (±5 minutes) and 4 hours (±15 minutes) postdose.

[g] Baseline visit 12-lead ECGs are triplicate and will be measured approximately 5 minutes apart. Recordings will be obtained after the patient has rested comfortably in the supine position for approximately 10 minutes. Patients should remain supine between ECGs. ECGs should be obtained at visits to the clinical study center where indicated in the Schedule of Assessments prior to study drug administration (see Section 7.4.4). ECGs do not need to be conducted for interim doses. After Month 12, ECGs will be performed at Months 24, 36, 48, and 54; all postbaseline ECGs will be measured in singlicate.

[h] Echo should be performed at Baseline only if the most recent echo was performed ≥30 days before Day 1. Echo will be performed during the first 12 months only.

[i] Pregnancy tests will be performed for women of childbearing potential only. Pregnancy testing should be performed prior to each dose; results of the pregnancy test must be known before ALN-GO1 administration. A serum pregnancy test will be performed at Baseline or after the onset of menarche if the patient was not of childbearing potential at Baseline, and urine pregnancy tests will be performed thereafter, and any time pregnancy is suspected. Patients who become pregnant should inform the clinical study center as soon as a pregnancy is confirmed.

[j] Clinical laboratory tests will be evaluated by a central laboratory.

[k] Study drug will be administered via SC injection. In patients whose disease progression requires a dialysis regimen, patients will continue on their current dosing regimen (see Section 6.2.2).

[l] Blood and urine samples for PK analysis will be obtained at the time points listed in Table 5.

[m] During the Baseline visit, the blood sample for PD analysis must be collected within 1 hour predose. In patients who progress to requiring dialysis, when a dialysis session is on same day as scheduled visit, the blood sample for PD analysis must be collected predialysis.

[n] Single, 24-hour urine sample collections will be performed before dosing, as indicated. For study visits through the Month 12 visit, urine collections should be completed within 7 days before each study visit. For study visits after the Month 12 visit (ie, Month 18 through the EOS) urine collections should be completed within 14 days before each study visit.

[o] QOL questionnaires include the KDQOL-36 for adults (age ≥18 years at Screening), and the PedsQL (the generic and ESRD modules) for children (age <18 years at screening).

[p] After Month 12, renal ultrasound will be performed at Months 24, 36, 48, and 54 (see Section 7.4.6).

[q] Events occurring or continuing after the completion of follow-up of Study ALN-GO1-001 and before first study drug administration in ALN-GO1-002 will be captured as medical history. Events that occur after first study drug administration, and baseline events that worsen after first study drug administration in ALN-GO1-002, must be recorded and reported as AEs.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AGT	Liver peroxisomal enzyme alanine-glyoxylate aminotransferase
AGXT	*Alanine glyoxylate aminotransferase*
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
C_{max}	Maximum plasma concentration
CL/F	Apparent clearance
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
eCRF	Electronic case report form
ECG	Electrocardiogram
Echo	Echocardiography
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study (visit)
EOT	End of Treatment (visit)
ESRD	End-stage renal disease
Fe	Fraction of drug excreted in urine
FSH	Follicle-stimulating hormone
GalNAc	*N*-acetyl galactosamine
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GO	glycolate oxidase
HAO1	Hydroxyacid oxidase 1
HCV	Hepatitis C virus

Abbreviation	Explanation
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISRs	Injection site reactions
KDQOL	Kidney Disease Quality of Life Questionnaire
LFT	Liver function test
MDRD	Modification of Diet in Renal Disease (formula)
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NHP	Non-human primate
PD	Pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PH1	Primary hyperoxaluria type 1
PK	Pharmacokinetics
QOL	Quality of life
QTcB	Bazett-corrected QT interval
QTcF	Fridericia corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
siRNA	Small interfering ribonucleic acid
SOC	System Organ Class
SRC	Safety Review Committee
SUSARs	Suspected unexpected serious adverse reactions
$t_{½\beta}$	Elimination half-life
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
V/F	Apparent volume of distribution
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1. Disease Overview

Alnylam Pharmaceuticals is developing lumasiran (ALN-GO1), a synthetic, small interfering RNA (siRNA) therapeutic directed against hydroxyacid oxidase 1 (*HAO1*) messenger RNA (mRNA), which is covalently linked to a ligand containing 3 *N*-acetylgalactosamine residues. ALN-GO1 is currently in development for the treatment of primary hyperoxaluria type 1 (PH1).

PH1 is a rare, autosomal recessive disease characterized by excessive production of oxalate and consequent hyperoxaluria. Given the relative insolubility of oxalate, it crystallizes in the urinary tract, primarily as calcium oxalate. This results in recurrent nephrolithiasis and/or nephrocalcinosis, with progressive renal disease leading to renal failure.[Cochat and Rumsby 2013] As renal function declines, calcium oxalate is deposited systemically, with consequent end organ damage. This stage of the disease, called systemic oxalosis, arises when the glomerular filtration rate (GFR) has declined to below 30 to 45 mL/min per 1.73 m^2.[Cochat and Rumsby 2013]

PH1 is caused by mutations in both alleles of the alanine glyoxylate aminotransferase (*AGXT*) gene, which encodes the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). Over 150 mutations in *AGXT* have been described. There are broad genotype–phenotype associations, notably in the responsiveness of disease caused by some mutations, to treatment with pyridoxine (vitamin B6). However, disease phenotype can be highly variable, including the responsiveness to vitamin B6 treatment, even within families.[Hopp 2015]

Given the rarity and heterogeneity of PH1, many patients go undiagnosed for years after the initial clinical manifestations of the disease. The incidence of PH1 is approximately 1 in 120,000 live births, and the prevalence is 1 to 3 per million in North America and Europe.[Cochat and Rumsby 2013; Hopp 2015; Hoppe 2010] The disease is more prevalent in areas where consanguineous marriages are common, especially in the Middle East and Northern Africa.[Al-Eisa 2004; Kamoun and Lakhoua 1996]

PH1 is primarily a pediatric disease, with symptoms first appearing in approximately half (48.6%) of the patients in the Rare Kidney Stone Consortium Primary Hyperoxaluria Registry between birth and four years of age. Approximately three-quarters of patients (74.7%) showed signs or symptoms before the age of 15 and 83.5% showed symptoms before 20 years of age. In comparison, only 16.5% of patients first displayed symptoms after age 20. Additionally, nearly one third (29.9%) of patients were diagnosed between birth and four years of age and two-thirds (66%) were diagnosed before 20 years of age.[Atlas 2007] The majority of patients are, therefore, diagnosed as children, and consequently, are more likely to have some preservation of renal function at time of diagnosis.

Most PH1 patients exhibit urinary oxalate excretion greater than 2-fold the upper limit of normal (ULN), although patients with severely compromised renal function may have lower excretion rates. PH1 is definitively diagnosed by gene sequencing to detect pathological mutations in *AGXT*, or by evaluation of AGT enzymatic activity in liver tissue obtained by biopsy.

Currently, there are no approved therapies for the treatment of PH1. Disease management is based on supportive measures, including high fluid intake, potassium citrate (to increase urinary oxalate solubility), vitamin B6, and treatment of complications such as urinary tract stones and

infections. Dietary modification plays a minor role in treatment since endogenous oxalate production far exceeds dietary intake. Patients progressing to or presenting with end-stage renal disease (ESRD) require intense kidney dialysis. However, dialysis, day and night, 6 days per week, may be inadequate to effectively offload accumulating oxalate.[Cochat 2012] Combined liver/kidney transplantation offers potentially curative therapy, but with limited availability, the attendant medical risks, and intense use of health care resources. Therefore, there is a high unmet medical need for additional treatments for patients with PH1. The deterioration of renal function that occurs in PH1 disease indicates the importance of investigating potentially disease-modifying interventions as early as possible after diagnosis.

1.2. ALN-GO1

ALN-GO1 (containing siRNA drug substance ALN-65585) is an investigational medicinal product that comprises a synthetic siRNA that specifically targets the mRNA of the *hydroxyacid oxidase* (*HAO1*) gene which encodes glycolate oxidase (GO). The drug substance is conjugated to an N-Acetyl galactosamine ligand (GalNAc) to facilitate targeted delivery to the liver and formulated in Water for Injection.

1.3. Study Design Rationale

This is a Phase 2, multicenter, open-label, extension study to evaluate the long-term administration of ALN-GO1 in patients with PH1. Within 12 months of completing Study ALN-GO1-001, patients may enroll in this study to receive open-label treatment with ALN-GO1 for approximately 4.5 years. Safety and efficacy assessments will be performed periodically as outlined in the Schedule of Assessments (Table 1).

1.4. Dose Rationale

Patients will initially receive ALN-GO1 at the same dose and regimen they received in Study ALN-GO1-001. Based on emerging data, the Safety Review Committee (SRC) can authorize an alteration of dose and/or dose regimen to one that is no higher than the highest dose evaluated in either Part A or Part B of Study ALN-GO1-001. This alteration may apply to subsequent doses for patients already enrolled and previously dosed in the study and/or to the initial dose and regimen for patients who have not yet been dosed in this study.

1.5. Benefit-Risk Assessment

ALN-GO1 is designed to reduce hepatic production of oxalate. The potential benefit of this treatment is the amelioration of the clinical course of PH1 in patients across the spectrum of disease, irrespective of age and disease stage. While the clinical benefit of long-term treatment with ALN-GO1 is unknown at present, it is anticipated that long term suppression of urinary oxalate excretion with ALN-GO1 could provide meaningful benefit. The potential risks of ALN-GO1 include pathway- and disease-specific risks, and non-specific, off-target risks.

Reduction of GO is expected to lead to reduction in hepatic oxalate production at the expense of increased glycolate, an organic acid. Therefore, study drug-induced increases in plasma and urine glycolate levels are anticipated in patients administered ALN-GO1. Since elevated levels of this organic acid are expected to be readily buffered, and its high solubility is not expected to result in crystallization in the urinary tract, the potential risk of increased glycolate production is

considered low. Importantly, no toxicity has been observed in non-human primate (NHP) pharmacology and toxicology studies, where profound suppression of hepatic GO, with associated increases in plasma glycolate levels, has been demonstrated. In particular, maintenance of normal serum bicarbonate levels in these animals indicates that there is no evidence of acidosis. Finally, a recent clinical case study described a child with an incidentally discovered homozygous defect in *HAO1*, the gene encoding GO. The patient exhibited marked elevations of urine glycolate, but no associated metabolic abnormalities and normal renal and hepatic function.[Frishberg 2014]

The potential for negative consequences of ALN-GO1 administration to patients with impaired renal function, including those with ESRD, is considered low. ALN-GO1, in common with other Sponsor-developed RNA interference compounds, is conjugated to N-acetyl galactosamine (GalNAc) to enable rapid and specific uptake by hepatocytes via the asialoglycoprotein receptor. Clinically effective doses of ALN-GO1 are not expected to saturate this receptor-mediated uptake or to result in enhanced extra-hepatic uptake or significant extra-hepatic exposure via accumulation.

Study assessments and visits have been reduced as much as possible to minimize the burden of the study on children without risking patient safety. The potential benefit to children enrolled in this study includes possible reduction in oxalate production during the study period, which may have an ameliorating effect on the course of their disease. In addition, experience in children with this disease under carefully controlled conditions will provide data that may enhance the future development of this therapeutic.

Non-specific potential risks to patients include: embryofetal risk, injection site reactions (ISRs), and liver function test (LFT) abnormalities.

No data are available on the use of ALN-GO1 in pregnancy or while breastfeeding; however, there is no implication of human teratogenicity based on class effects or genotoxic potential. Embryofetal risk is limited by requiring that women of childbearing potential (WOCBP) must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception as specified in the protocol. No male contraception is considered to be required.

ALN-GO1 is administered subcutaneously, and occurrence of ISRs will be carefully monitored.

As ALN-GO1 is a hepatically-targeted therapeutic, and although nonclinical data suggest that there is a wide margin between the proposed clinical doses and any hepatic findings in toxicology studies, LFTs will be carefully monitored.

During the course of this study, safety will be monitored by study Investigators, the Sponsor Medical Monitor, and a SRC.

Overall, in this clinical study of ALN-GO1, the benefit-risk assessment is favorable in patients with PH1. The suppression of urinary oxalate excretion with ALN-GO1 may provide a pharmacological benefit.

The dose or dose regimen used in this study may be adjusted based on emerging data to enable an optimal pharmacodynamic (PD) effect that is well tolerated.

A summary of the clinical and nonclinical data relevant to the investigational drug and its study in human subjects is provided in the Investigator's Brochure.

2. OBJECTIVES

2.1. Primary Objective

- Evaluate the long-term safety of multiple doses of ALN-GO1 in patients with PH1

2.2. Secondary Objectives

- Evaluate the PD effect of ALN-GO1 on urinary oxalate excretion
- Characterize the effect of ALN-GO1 on markers of renal function

2.3. Exploratory Objectives

- Characterize the pharmacokinetics (PK) of ALN-GO1
- Evaluate the PD effect of ALN-GO1 on urinary glycolate excretion, plasma oxalate concentration, plasma glycolate concentration, and urine oxalate:creatinine ratio
- Evaluate the incidence of anti-drug antibodies (ADA)

3. ENDPOINTS

3.1. Primary Endpoint

- Incidence of adverse events (AEs)

3.2. Secondary Endpoints

- Change in 24-hour urinary oxalate corrected for body surface area (BSA) over time
- Change in 24-hour urinary oxalate:creatinine ratio over time
- Change in estimated glomerular filtration rate (eGFR) over time

3.3. Exploratory Endpoints

- Describe the effects of ALN-GO1 on other safety parameters, including assessments of vital signs, electrocardiograms (ECG), renal ultrasounds, clinical laboratory parameters, and physical examinations.
- Assess ALN-GO1 plasma PK parameters including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), fraction of drug excreted in urine (Fe), apparent clearance (CL/F), and apparent volume of distribution (V/F).
- Change from Baseline over the course of the study in the following PD parameters:
  - Urinary glycolate excretion
  - Plasma oxalate concentration
  - Plasma glycolate concentration

  - Spot urinary oxalate:creatinine ratio
- Incidence of ADA

4. INVESTIGATIONAL PLAN

4.1. Summary of Study Design

This is a multicenter, open-label extension study to evaluate the long-term safety, PK, and PD of subcutaneously administered ALN-GO1 in patients with PH1 who completed Study ALN-GO1-001.

Consented eligible patients will enroll in this study and initially receive subcutaneous (SC) injections of ALN-GO1 at the same dose and regimen as they received in Study ALN-GO1-001. Based on emerging data, the SRC may authorize an alteration of dose and/or dose regimen to one that is no higher than the highest dose evaluated in either Part A or Part B of Study ALN-GO1-001. If such an authorization occurs, dose and/or dose regimen alteration may occur for an individual patient or entire cohort. This alteration may apply to subsequent doses for patients already enrolled and previously dosed in the study and/or to the initial dose and regimen for patients who have not yet been dosed in this study. Patients will be assessed for safety at each study visit.

PD assessments will be completed quarterly over the first 12 months on study, and approximately every 6 months thereafter for the study duration. PK assessments will be conducted during the first 12 months on study (Table 1).

Patients may receive ALN-GO1 as long as they do not fulfill any of the study discontinuation criteria (see Section 5.3.1) or until ALN-GO1 is commercially available in the patient's territory or the ALN-GO1 development program is discontinued (whichever comes first).

4.2. Duration of Treatment

The estimated duration of treatment in this study is up to 54 months.

4.2.1. Definition of the End of Study for an Individual Patient

The End of Treatment (EOT) visit is defined as the visit when the final dose of ALN-GO1 is administered. The End of Study (EOS) visit is defined as the visit 3 months after the EOT. Patients are considered to have completed the study when they have completed the EOS visit.

Patients who discontinue treatment but remain on study for assessments are considered to have reached the end of the study upon completing 6 months of monitoring following the final dose of ALN-GO1.

For patients who withdraw from the study, see Section 5.3.2.

4.3. Number of Patients

Up to 20 patients are planned for enrollment in this study.

4.4. Method of Assigning Patients to Treatment Groups

Not applicable. This is an open-label study.

4.5. Blinding

Not applicable. This is an open-label study.

4.6. Safety Review Committee

An SRC will perform ongoing reviews of safety, tolerability, and available study data collected in this study with the primary purpose of protecting the safety of patients. At a minimum, reviews will be conducted every 3 months.

The SRC will be comprised of the Sponsor Medical Monitor, a Medical Monitor from the contract research organization (CRO), 3 Investigators from participating clinical study centers or their designees, and an independent pediatrician experienced in clinical investigation who is not a study investigator.

The SRC is governed by a charter that was signed prior to enrollment of the first subject.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Enrollment within 12 months of completion of Study ALN-GO1-001 and in the opinion of the investigator, tolerated the study drug
2. If taking vitamin B6 (pyridoxine), willing to remain on a stable regimen for the study duration
3. Women of child-bearing potential must have a negative pregnancy test, cannot be breast feeding, and must be willing to use a highly effective method of contraception from 14 days before first dose and throughout study participation until the completion of the follow-up period
4. Willing and able to comply with the study requirements and to provide written informed consent and assent in the case of patients under the age of legal consent, per local and national requirements

5.2. Exclusion Criteria

Each patient must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Any uncontrolled or serious disease, or any medical or surgical condition (with the exception of PH1) that may either interfere with participation in the clinical study, and/or put the patient significant risk (according to the Investigator's judgment) if he/she participates in the clinical study

2. An underlying known disease or surgical or medical condition (with the exception of PH1) that in the opinion of the investigator might interfere with the interpretation of the clinical study results
3. Requirement for chronic dialysis
4. Triplicate 12-lead ECG with clinically significant abnormalities at Baseline visit, at the discretion of the investigator
5. Echo assessment of abnormal left ventricular systolic function, defined as left ventricular ejection fraction <55% at Screening
6. Abnormal for aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and any other clinical safety laboratory result considered clinically significant and unacceptable by the Investigator at Baseline, at discretion of investigator
7. Legal incapacity or limited legal capacity at Screening of patient, parent, or legal guardian

5.3. Removal from Therapy or Assessment

Patients or their legal guardian (in case patient has not reached the age of majority) are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or withdrawal from the study must be fully documented in the electronic case report form (eCRF), and should be followed up by the Investigator. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

Discontinuation of study drug and withdrawal from the study are described in Section 5.3.1 and Section 5.3.2, respectively.

5.3.1. Discontinuation of Study Drug

The Investigator or designee may discontinue dosing in a patient if the patient:

- Is in violation of the protocol
- Experiences a serious or intolerable AE
- Becomes pregnant
- Is found to be considerably noncompliant with the protocol requirements

The Investigator will confer with the Sponsor or Medical Monitor before discontinuing dosing in the patient. Patients who are pregnant will be discontinued from dosing immediately (see Section 7.4.8.6 for reporting and follow-up of pregnancy). In general, patients who discontinue study drug dosing for any reason will be encouraged to complete the End of Treatment assessments and safety and PD follow up visits so that their experience is captured in the final analyses. Patients who discontinue study drug but who remain on study may receive local standard of care treatment for their disease, as applicable.

5.3.2. Withdrawal From Study

A patient/legal guardian may withdraw from the study at any time. If a patient/legal guardian chooses to withdraw from the study, every effort should be made to conduct the End of Treatment assessments and safety and PD follow-up visits (see Table 1).

When a patient withdraws from the study, the primary reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible. If a patient withdraws due to a serious adverse event (SAE), the SAE should be followed as described in Section 7.4.8. There will be no replacements of patients who withdraw from this study.

6. TREATMENTS

6.1. Treatments Administered

Study drug supplied for this study must not be used for any purpose other than the present study and must not be administered to any person not enrolled in the study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

6.2. Investigational Study Drug

Detailed information describing the preparation, administration, and storage of ALN-GO1 is provided in the Pharmacy Manual.

6.2.1. Description

ALN-GO1 is a synthetic, double-stranded small interfering RNA oligonucleotide directed against *HAO1* mRNA that is covalently linked to a ligand containing 3 *N*-acetylgalactosamine residues.

6.2.2. Dose and Administration

Initially, patients will receive SC injections of ALN-GO1 at the same dose and regimen as they received in Study ALN-GO1-001. Based on emerging data, the SRC may authorize an alteration of dose and/or dose regimen to one that is no higher than the highest dose evaluated in either Part A or Part B of Study ALN-GO1-001. If such an authorization occurs, dose and/or dose regimen alteration may occur for an individual patient or entire cohort. This alteration may apply to subsequent doses for patients already enrolled and previously dosed in the study and/or to the initial dose and regimen for patients who have not yet been dosed in this study.

Patients will be administered study drug by SC injection(s). The body weight obtained within 4 months before the study visit day or dosing day will be used for calculation of the ALN-GO1 dose to be administered.

Study drug will be administered under the supervision of the Investigator or designee. Detailed instructions for study drug administration are found in the Pharmacy Manual.

Dosing will be permitted at a location other than the study center (for example, the patient's home) by a healthcare professional with the oversight of the Investigator at all time points,

provided the patient has tolerated ALN-GO1 administered in the clinic. However, continued study drug administration at the study center should be considered for patients who have ongoing study drug-related AEs, worsening injection site reactions with repeat dosing, or for anyone in the opinion of the Investigator who would benefit from clinical observation following dosing.

If the patient is unable to come to the study site, and a visit by a healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, ALN-GO1 may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on ALN-GO1 administration prior to dosing. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes for dosing.

The sites of injection may be the abdomen, the upper arms, or thighs. If a local reaction around the injection site occurs, photographs may be obtained.

Patients whose disease progresses to requiring a dialysis regimen will continue on their planned dosing regimen. The ALN-GO1 dose will be administered as soon as feasible following the end of dialysis, eg, within 2 hours of completing the dialysis session. If a patient does not receive a dose of ALN-GO1 within the specified dosing window, the Investigator should contact the Medical Monitor. After such consultation, the dose may be administered or considered missed and not administered.

If a patient misses multiple doses of study drug, the Investigator, in consultation with the Medical Monitor, will discuss whether the patient will be able to continue on the study.

Additional details can be found in the Pharmacy Manual. In addition, instructions and procedures related to administration of ALN-GO1 by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

6.2.3. Dose Modifications

Dose modification is not permitted in this study, except as noted in Section 6.2.2.

If a study drug-related AE occurs in a patient that the Investigator judges as presenting a potential risk to the patient for further dosing, the study drug dose may be held at the discretion of the Investigator and the Medical Monitor should be contacted.

6.2.3.1. Liver Function Test Criteria for Withholding, Monitoring and Stopping Study Drug Dosing

1. LFT results from the previous visit should be reviewed prior to dosing.
2. For any ALT or AST elevation >3× ULN central laboratory results should be used to guide subsequent monitoring as detailed in Table 2.
3. For any ALT or AST elevation >3× ULN:
    a. If local laboratory results are obtained, confirm using central laboratory, as soon as possible, ideally within 2 to 3 days, but no later than 7 days.
    b. If an alternative cause is found, provide appropriate care.

c. If an alternative cause is not found, perform assessments per Table 2 and Table 4.

4. For any ALT or AST elevation >3× ULN without alternative cause that is accompanied by clinical symptoms consistent with liver injury (eg, nausea, right upper quadrant abdominal pain, jaundice) or elevated bilirubin to ≥2× ULN or INR ≥1.5, permanently discontinue dosing.
5. For confirmed ALT or AST elevations >3× ULN without alternative cause and not accompanied by symptoms or elevated bilirubin ≥2× ULN or INR ≥1.5, see Table 2 (below):

Table 2: Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3× ULN, with No Alternative Cause Identified

Transaminase Level	Action

>3× to 5× ULN	• May continue dosing
	• Evaluate the initial elevation in LFT per the following assessments:
	  • Table 4 (all assessments to be performed once)
	  • Hematology, serum chemistry and LFT per Table 3
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor LFTs at least every two weeks
	• If elevation persists for ≥2 months, must discuss with the medical monitor before continuing dosing

>5× to 8× ULN	• Hold study drug dosing until recovery to ≤1.5× ULN or baseline; may resume dosing after discussion with the Medical Monitor
	• Evaluate the initial elevation in LFT per the following assessments
	  • Table 4 (all assessments to be performed once)
	  • Hematology, serum chemistry and LFT per Table 3
	  • Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)
	• Monitor LFTs at least weekly until ALT and/or AST is declining on 2 consecutive draws, then may decrease monitoring to biweekly
	• If ALT or AST rises to >5× ULN following resumption of dosing, permanently discontinue dosing

>8× ULN	Permanently discontinue dosing after confirmation of the transaminase value at the central laboratory.

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; LFT=liver function test(s); ULN=upper limit of normal.
Notes: In addition to these criteria, other assessments or evaluations may be performed per Investigator discretion, as appropriate.

6.2.4. Preparation, Handling, and Storage

Staff at each clinical study center, or the healthcare professional performing administration at home, will be responsible for preparation of ALN-GO1 doses according to procedures detailed in the Pharmacy Manual. In cases where ALN-GO1 is administered at home by a patient/caregiver,

dosing may be prepared and administered by the patient/caregiver according to procedures detailed in the Patient/Caregiver Storage and Administration Instructions. No special procedures for the safe handling of study drug are required.

Study drug will be stored upright and refrigerated at approximately 5±3°C.

Instructions specific to unused study drug and additional storage will be provided in the Pharmacy Manual and the Patient/Caregiver Storage and Administration Instructions.

A Sponsor representative or designee will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

6.2.5. Packaging and Labeling

All packaging, labeling, and production of study drug will be in compliance with current Good Manufacturing Practice specifications, as well as applicable local regulations. Study drug labels and external packaging will include all appropriate information as per local labeling requirements. Additional details will be available in the Pharmacy Manual.

6.2.6. Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs.

Further instructions about drug accountability are detailed in the Pharmacy Manual.

6.3. Concomitant Medications

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

Standard vitamins and topical medications are permitted. However, topical steroids must not be applied anywhere near the injection site(s) unless medically indicated. Any treatment for an injection site reaction must be prescribed by the investigator or his/her designee.

Any concomitant medication that is required for the patient's welfare may be administered by the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded on the eCRF. Concomitant medication will be coded using an internationally recognized and accepted coding dictionary.

Patients may be treated for PH1 according to local standard of care. Patients can continue their current standard of care regimen, including hyperhydration, crystallization inhibitors, and/or pyridoxine therapy during the study. Standard of care treatment may be adjusted in accordance with clinical judgement.

6.4. Contraceptive Requirements

Women of child-bearing potential must be willing to use a highly effective method of contraception 14 days before first dose and throughout study participation until the completion of the follow-up period. Highly effective methods of birth control result in a low failure rate (ie, less than 1% per year). Birth control methods which may be considered as highly effective include:

- Established use of oral (except low-dose gestagens [eg, lynestrenol and norethisterone]), implantable, injectable, or transdermal hormonal methods of contraception
- Placement of an intrauterine device
- Placement of an intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients on the study, the vasectomized male partner should be the sole partner for that patient);
- True sexual abstinence, when in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study until the completion of the follow-up period.

WOCBP includes any female patient who has experienced menarche and who is not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). Postmenopausal state is defined as no menses for 12 months without an alternative medical cause, confirmed by follicle stimulating hormone (FSH) level within the postmenopausal range.

No male contraception is considered to be required. However, use of contraception (condom) by males may be required in some countries, eg, France, in order to comply with local requirements as described in the corresponding patient informed consent forms.

Compliance with contraception requirements will be assessed by the Investigator throughout the course of the study.

6.5. Treatment Compliance

Compliance with study drug administration will be verified by study staff.

7. STUDY ASSESSMENTS

The schedule of study assessments is provided in Table 1.

Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study

assessments, which may include pregnancy testing (as applicable), collection of blood and urine samples, measurement of vital signs, height and body weight, body system assessment, and preparation and administration of study drug (at the discretion of the Investigator) at all timepoints as specified in the Schedule of Assessments.

7.1. Screening/Baseline Assessments

The Screening and Baseline (Day -1/ Day 1) visits may be combined, if possible. The final visit in Study ALN-GO1-001 may be conducted with the Screening and Baseline visit in this protocol. If the final visit in Study ALN-GO1-001 is within 30 days of Day 1, then assessments required by both protocols do not need to be duplicated.

Patient demographic data will be obtained from Study ALN-GO1-001. Complete medical history will be obtained at screening and any changes will be updated on admission at the Baseline visit, if different from the Screening visit. Events occurring after signing of the informed consent or assent (if applicable) form and before study drug administration will be captured as medical history.

7.2. Pharmacodynamic and Renal Assessments

Urine and blood samples will be collected for assessment of PD parameters (oxalate and glycolate concentrations) at the time points in the Schedule of Assessments (Table 1). See 24-hour urine collection validity criteria in Section 7.2.1.

Patients will have the option to bring the 24-hour urine collections to the clinical study center at specified visits, courier samples to the clinical study center or to the vendor performing analyses, or elect to have the 24-hour urine collected during an inpatient stay at the clinical study center for other assessments.

Additionally, blood samples for measurement of eGFR will be obtained at the time points in the Schedule of Assessments (Table 1). eGFR (mL/min/1.73m^2) will be calculated to assess renal function during the study. The calculation will be based on the Modification of Diet in Renal Disease (MDRD) formula for patients ≥18 years of age at Screening and the Schwartz Bedside Formula for patients <18 years of age at Screening.[Levey 2009; Schwartz 2009]

Blood samples will be collected predose for plasma oxalate assessment in all patients, as specified in the Schedule of Assessments. In patients who have disease has progressed to requiring dialysis, if dialysis session is on same day as scheduled visit, blood samples for assessment of plasma oxalate will be collected pre-dialysis. In addition to plasma oxalate assessment, in patients on dialysis who are not anuric (ie, patients who are able to continue to produce urine ≥100 ml per day) 24-hour urinary oxalate excretion will continue to be assessed.

Biologic samples for biomarker research and possible metabolic profiling can be retained on behalf of the Sponsor for a maximum of 15 years following the last patient's last visit in the study.

Details regarding the processing and aliquoting of samples for storage and PD analyses are provided in the Laboratory Manual.

7.2.1. Validity Criteria for 24-hour Urine Collections

24-hour urine collections will be performed as specified in the Schedule of Assessments (Table 1). Any or all of the 24-hour urine collections may be conducted supervised. If 24-hour urine is not a supervised collection, patients may either bring 24-hour urine collections to the clinic or have it couriered to the designated laboratory.

If collection does not meet the validity criteria specified below, a single repeat collection should be obtained within ±14 days of the visit day. The dose does not need to be held if validity results are unknown prior to dosing.

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

- The collection is between 18-26 hours in duration between the initial discarded void and the last void or attempt to void.
- No voids are missed between the start and end time of the collection as indicated by the patient's urine collection record.
- The 24-hour creatinine content is at least 10 mg/kg as assessed by the central laboratory.

A single repeat collection as specified above, does not need to be obtained within ±14 days for patients on dialysis.

7.3. Pharmacokinetic Assessments

Blood and urine samples will be collected for assessment of ALN-GO1 PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments (Table 1). A detailed schedule of time points for the collection of blood samples for PK analysis is in Table 5 in Appendix 11.1.

The concentration of ALN-GO1 will be determined using a validated assay. Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

7.4. Safety Assessments

The assessment of safety during the course of the study will consist of the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication and measurements of vital signs, weight and height, physical examination and ECG findings, and clinical laboratory tests. Echocardiograms and renal ultrasounds will also be assessed.

Safety will be monitored over the course of the study by an SRC as described in Section 4.6.

7.4.1. Vital Signs

Vital sign measurements include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be measured in the supine or seated position, after the patient has rested comfortably for approximately 10 minutes. Blood pressure should be taken using the same arm. Body temperature in degrees Celsius will be obtained via oral, tympanic, or axillary methods. Heart rate will be counted for a full minute and recorded in beats per minute, and respiration rate will be counted for a full minute and recorded in breaths per minute.

Vital sign measurements will be performed as specified in the Schedule of Assessments (Table 1). For the safety of the patient, additional vital sign assessments may be added at the discretion of the Investigator.

7.4.2. Weight and Height

During the Baseline visit and at EOT, height will be measured in centimeters in triplicate for all patients; for all other study visits height will only be measured for patients <18 years of age. For patients <18 years of age, at each time point, height will be measured in centimeters, and in triplicate, to facilitate calculation of eGFR using the Schwartz Bedside formula.

7.4.3. Physical Examination

Full physical examinations will include the examination of the following: general appearance, head, eyes, ears, nose and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological/psychiatric.

A symptom-directed physical examination will include only those organ systems necessary for the evaluation of changes in symptoms, or the onset of new symptoms, since the last visit.

If a study visit occurs at a location other than the study center, a body system assessment may be performed in lieu of a physical examination.

Physical examinations will be performed as specified in the Schedule of Assessments (Table 1).

7.4.4. Electrocardiogram

At Baseline, triplicate 12-lead ECGs will be measured 5 minutes apart. Recordings will be obtained after the subject/patient has rested comfortably in the supine position for approximately 10 minutes. Patients should remain supine between ECGs. ECGs should be obtained at visits to the clinical study center according to the Schedule of Assessments (see Table 1) prior to study drug administration. At all post-baseline visits, ECGs will be measured in singlicate, and obtained predose. ECGs do not need to be conducted for interim doses.

Additional ECGs may be collected at the discretion of the Investigator. The electrophysiological parameters assessed will include, but are not limited to, rhythm, ventricular rate, PR interval, QRS duration, QT interval, ST and T waves, Bazett-corrected QT interval (QTcB) and Fridericia corrected QT interval (QTcF).

The Investigator or designee is responsible for reviewing the ECGs to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. For any clinically significant changes from the Baseline visit (eg, ischemic ECG changes, wave/interval changes, or arrhythmia), the Investigator must contact the Medical Monitor to discuss continued participation of the subject/patient in the study.

After Month 12, ECGs will be performed at Months 24, 36, 48, and 54 only. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, ECGs may be completed up to 9 months after the intended time point.

7.4.5. Echocardiography

Echo assessments will be performed as specified in the Schedule of Assessments (Table 1), and according to instructions provided in a study manual. The Investigator or designee is responsible for reviewing the echos to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. For any clinically significant changes from the Baseline visit, the Investigator must contact the Medical Monitor.

7.4.6. Renal Ultrasound

Renal ultrasound will be performed according to instructions provided in a study manual. The Investigator or designee is responsible for reviewing the renal ultrasound to assess whether the results have changed since the Baseline visit and to determine the clinical significance of the results. For any clinically significant worsening from the Baseline visit, the Investigator must contact the Medical Monitor.

After Month 12, renal ultrasound will be performed at Months 24, 36, 48, and 54 only. During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, renal ultrasounds may be completed up to 9 months after the intended time point.

7.4.7. Clinical Laboratory Assessments

The following clinical laboratory tests will be evaluated by a central laboratory. Specific instructions for transaminase elevations are provided in Section 6.2.3.1. For any other unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator, and in conjunction with the Medical Monitor if feasible, or as per SRC advice, until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality. Additional safety laboratory assessments as indicated by the clinical situation may be requested. Clinical laboratory assessments are listed in Table 3 and will be assessed as specified in the Schedule of Assessments (Table 1). While local laboratory results may be used for urgent clinical and dosing decisions, on the day of the clinic visit assessments, all laboratory assessments specified in the following table which are performed at the clinic should also be sent in parallel to the central laboratory, blood volumes permitting. Central laboratory results (once available) should be used for subsequent clinical and dosing decisions in the case of discrepant local and central laboratory results of samples drawn on the same day.

For any safety event or laboratory abnormality, additional laboratory assessments, imaging, and consultation may be performed for clinical evaluation and/or in consultation with the Medical Monitor, or as per SRC advice; results may be collected and included in the clinical database. Clinical laboratory assessments may be collected at the clinical site or at a location other than the clinical study center by a trained healthcare professional, where applicable country and local regulations and infrastructure and allow.

Table 3: Clinical Laboratory Assessments

Hematology
Complete blood count with differential
Serum Chemistry

Sodium	Potassium
BUN	Phosphate
Creatinine and eGFR (using the MDRD formula for adults (≥18 years of age) or the Bedside Schwartz formula for Children <18 years)	Albumin
Uric acid	Calcium
Total protein	Carbon dioxide
Glucose	Chloride
Liver Function Tests	
AST	ALP
ALT	Bilirubin (total and direct)
Urinalysis	
Visual inspection for appearance and color	Bilirubin
pH (dipstick)	Nitrite
Specific gravity	RBCs
Ketones	Urobilinogen
Albumin	Leukocytes
Glucose	Microscopy (if clinically indicated)
Protein	
Pregnancy Testing (WOCBP only)	
β-human chorionic gonadotropin	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; MDRD=modification of diet in renal disease; WOCBP=women of child-bearing potential.

7.4.7.1. Immunogenicity

Blood samples will be collected to evaluate ADA. Blood samples for ADA testing must be collected before study drug administration.

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

7.4.7.2. Pregnancy Testing

A pregnancy test will be performed for WOCBP only. A serum pregnancy test will be performed at Baseline and urine pregnancy tests will be performed thereafter per the Schedule of Assessments (Table 1) and at any time pregnancy is suspected. Pregnancy testing may be performed offsite by a patient/caregiver if the patient/caregiver will be administering the study drug. The results of the pregnancy test must be known before study drug administration. Patients who are pregnant are not eligible for study participation. Any woman with a positive pregnancy test during the study will be discontinued from study drug but will continue to be

followed for safety. Patients determined to be pregnant while on study will be followed until the pregnancy outcome is known (see Section 7.4.8.6 for follow-up instructions).

7.4.7.3. Additional Liver Function Assessments

Additional laboratory assessments will be performed in patients who experience any LFT abnormalities as outlined in Section 6.2.3.1. Following the occurrence of elevated liver transaminases or other LFT abnormalities per central laboratory without an alternative cause identified, all assessments in Table 4 will be performed one time, as well as hematology, serum chemistry, and LFT assessments from Table 3, and coagulation and other assessments or evaluations per Investigator discretion, as appropriate.

Monitoring, including criteria for withholding the study drug, are described in Section 6.2.3.1.

Table 4: Hepatic Assessments in Patients Who Experience Elevated Transaminases

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

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBc=hepatitis B core; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; HHV-6=human herpesvirus 6; HIV=human immunodeficiency virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; MRI=magnetic resonance imagery; PCR=polymerase chain reaction; RNA=ribonucleic acid.
Note:

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

[a] HIV testing will not be performed where prohibited by local regulations.

7.4.7.4. Maximum Blood Volume

The maximum blood volume, which will be collected from pediatric patients over the course of the study, will be based on age and weight and will not exceed those specified in Table 6 from

the Feinstein Institute for Medical Research Human Subject Protection Program Guidance Document (Section 11.2 in the Appendix).[Feinstein Institute 2013]

7.4.8. Adverse Events

7.4.8.1. Definitions

Adverse Event

According to the International Conference on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

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

Adverse Event Severity

Adverse events are to be graded according to the categories detailed below:

Mild:	Mild events are those which are easily tolerated with no disruption of normal daily activity.
Moderate:	Moderate events are those which cause sufficient discomfort to interfere with normal daily activities.
Severe:	Severe events are those which incapacitate and prevent usual activity.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence. When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day

should be noted. If the severity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates)

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for Serious Adverse Event).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study treatment should be evaluated by the Investigator using the following criteria:

Definitely related:	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.
Possibly related:	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.
Unlikely related:	A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
Not related:	A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.

Adverse Events of Clinical Interest

The following are considered to be AEs of clinical interest:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN)
- Severe or serious injection site reactions (ISRs); ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections), or those that lead to temporary dose interruption or permanent discontinuation of study drug.

  An ISR is defined as a local reaction at or near the site of injection. "At or near" the injection site includes reactions at the injection site, adjacent to the injection site, or a reaction which may shift slightly away from the injection site due to gravity (eg, as may occur with swelling or hematoma). A systemic reaction which includes the injection site, eg, generalized urticaria, other distinct entities or conditions like lymphadenopathy that may be near the injection site is not considered an ISR.

These AEs will be recorded both on a supplemental eCRF and on an Adverse Event of Clinical Interest form. Refer to the eCRF completion guidelines for details.

7.4.8.2. Eliciting and Recording Adverse Events

Eliciting Adverse Events

The patient should be asked about medically relevant changes in his/her health since the last visit. The patient should also be asked if he/she has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and over-the-counter). In addition to patient observations, AEs will be documented from any clinically relevant laboratory findings, physical examination findings, electrocardiogram changes, or other findings that are relevant to patient safety.

Recording Adverse Events

The Investigator is responsible for recording non-serious AEs that are observed or reported by the patient after administration of the first dose of study drug regardless of their relationship to study drug through the end of study. Non-serious AEs will be followed until the end of study.

The Investigator is responsible for recording SAEs that are observed or reported by the patient after the time when the informed consent is signed regardless of their relationship to study drug through the end of study. SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the Investigator to be chronic or the patient is stable, as appropriate.

All AEs must be recorded in the source records for the clinical study center and in the eCRF for the patient, whether or not they are considered to be drug-related. Each AE must be described in detail: onset time and date, description of event, severity, relationship to investigational drug, action taken, and outcome (including time and date of resolution, if applicable).

For SAEs, record the event(s) in the eCRF. If the electronic data capture (EDC) system is unavailable, complete the back-up SAE form.

For AEs that are considered AEs of clinical interest, additional clinical information may be collected based upon the severity or nature of the event. Refer to CRF completion guidelines for details on reporting events in the supplemental eCRF.

For all ISRs, the Investigator, or delegate, should submit an Injection Site Reactions Signs or Symptoms eCRF, recording additional information (eg, descriptions, onset and resolution date, severity, treatment given, and event outcome).

In some cases, where it is medically appropriate, further evaluation may include photographs, referral to a dermatologist, skin biopsy, or other laboratory testing. If a biopsy was obtained, the Sponsor may request that the biopsy also be reviewed by a central dermatopathologist. To better understand the safety profile of the study drug, additional analysis of biopsy tissue may be performed as permitted by local regulations. Refer to the CRF completion guidelines for details on the form(s).

7.4.8.3. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the SAE criteria in Section 7.4.8.1 must be reported to the Sponsor or designee within 24 hours from the time that clinical study center staff first learns of the event. All SAEs must be reported regardless of the relationship to study drug.

The initial report should include at least the following information:

- Patient's study number
- Description and date of onset of the event
- Criterion for serious
- Preliminary assignment of relationship to study drug, and
- Investigator/site information

To report the SAE, complete the eCRF. If the EDC system is unavailable, complete the back-up SAE form. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form. SAEs must be reported using the contact information provided in the Study Binder.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

7.4.8.4. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for suspected unexpected serious adverse reactions (SUSARs) and other reportable events:

Immediately and within 7 calendar days

- Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and fatal or life threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days

- Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and serious, but not fatal or life threatening, and there is evidence to suggest a causal relationship between the study drug and the reaction.
- Any finding from tests in laboratory animals that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the study patients.

In addition, periodic safety reporting to regulatory authorities will be performed by the Sponsor or its representative according to national and local regulations.

7.4.8.5. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

SUSARs will be reported to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) per their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

7.4.8.6. Pregnancy Reporting

If a female patient becomes pregnant during the course of this study, the Investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the Investigator until completion. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, then the Investigator should follow the procedures for reporting an SAE as outlined in Section 7.4.8.3.

7.4.8.7. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than included in the protocol. It is up to the investigator to decide whether a dose is to be considered an overdose, in consultation with the Sponsor. Overdose must be recorded in the eCRF.

All reports of overdose (with or without an AE) must be reported within 24 hours to the Sponsor or designee.

7.4.9. COVID-19 Data Collection

Information on the coronavirus disease 2019 (COVID-19) infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.

7.5. Other Assessments

7.5.1. Quality of Life (QOL)

QOL will be assessed using the KDQOL, specifically the KDQOL-36[Rand Health Care 2000] for patients ≥18 years of age at Screening, and the PedsQL, including the generic and ESRD modules (parent and/or self-report versions)[Goldstein 2008; Varni 1999] for patients <18 years of age at Screening. After Month 12, QOL questionnaires will not be collected (see the Schedule of Assessments, Table 1).

8. STATISTICS

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

8.1. Determination of Sample Size

Sample size is not determined through a power calculation but based on the number of patients who complete Study ALN-GO1-001 and are eligible to enroll in this study.

8.2. Statistical Methodology

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified as needed in the clinical study report. Additional data summaries to help understand any impact of COVID-19 on safety and efficacy assessments will be outlined in the SAP.

8.2.1. Populations to be Analyzed

The safety analysis set will include all patients who received at least 1 dose of study drug. Patients with missing PD or PK data will be excluded from the PK/PD analyses as appropriate.

8.2.2. Examination of Subgroups

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

8.2.3. Handling of Missing Data

Unrecorded values will be treated as missing. The appropriateness of the method(s) described for handling missing data may be reassessed and documented in the SAP prior to database lock. Depending on the extent of missing values, further investigation may be made into the sensitivity of the analysis results to the method(s) specified.

8.2.4. Baseline Evaluations

Demographics and other baseline characteristics will be summarized. Descriptive statistics for age, race, ethnicity, gender, height, body weight, and BMI will be provided.

8.2.5. Pharmacodynamic Analysis

PD analysis will be based on the change from baseline over the course of the study in the following PD parameters:

- eGFR
- 24-hour urinary oxalate corrected for BSA
- Urinary glycolate excretion
- Plasma oxalate concentration

- Plasma glycolate concentration
- 24-hour and spot urinary oxalate:creatinine ratio

The PD parameters will be summarized using descriptive statistics for actual results and relative to baseline for each follow-up time points.

For the parameter eGFR, the change from baseline over the course of the study will be summarized using descriptive statistics for actual results and relative to baseline for each follow-up time points.

8.2.6. Pharmacokinetic Analysis

Pharmacokinetic analyses will be conducted using noncompartmental methods.

Pharmacokinetic parameters include, but will not be limited to: C_{max}, t_{max}, $t_{½\beta}$, AUC, Fe, CL/F, and V/F. Other parameters may be calculated, if deemed necessary.

8.2.7. Anti-drug Analyses

Anti-drug antibody results will be summarized descriptively. A by-patient data listing will also be provided.

8.2.8. Safety Analyses

Extent of exposure will be summarized. Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term. Prior and concomitant medications will be classified using an internationally recognized and accepted coding dictionary.

Incidence of AEs (those events that started after exposure to study drug or worsened in severity after dosing) will be presented. Incidence of AEs will also be presented by maximum severity and relationship to study medication. The incidence of SAEs and AEs leading to discontinuation of treatment will also be tabulated. By-patient listings will be provided for deaths, SAEs, and events leading to discontinuation of treatment. Additional tabular summaries of AEs may be presented by other grouping including, but not limited to high level term (HLT), high level group term (HLGT), or standardized MedDRA query (SMQ).

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Laboratory shift tables from baseline to worst values will be presented. Abnormal physical examination findings, renal ultrasound, ECG, and echo data will be presented in by-patient listings.

Descriptive statistics will be provided for electrocardiogram interval data and presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Details of any abnormalities will be included in patient listings.

8.2.9. Other Analyses

QOL questionnaires are not required after Month 12. No change from baseline analyses are planned for the QOL questionnaires; listings will be provided.

8.2.10. Interim Analysis

There is no formal interim analysis planned for this open-label study. Interim data examinations may be performed and will generally be descriptive in nature. Interim data from the study may be presented at scientific meetings.

9. STUDY ADMINISTRATION

9.1. Ethical and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

9.1.1. Informed Consent

The Investigator will ensure that the patient/legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients/Legal guardians must also be notified that they are free to discontinue from the study at any time. The patient/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided. In the case of patients under the age of legal consent, legal guardian(s) must provide informed consent and the patient should provide assent per local regulations and institutional standards.

The patient's/legal guardian's signed and dated informed consent (or assent, if applicable) must be obtained before conducting any study procedures.

The Investigator must maintain the original, signed Informed Consent Form or Assent Form (if applicable). A copy of the signed Informed Consent Form (or assent, if applicable) must be given to the patient/legal guardian.

The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented.

9.1.2. Ethical Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study (except those that support the need to remove an apparent immediate hazard to the patient). The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Initial IRB approval of the protocol, and all materials approved by the IRB for this study including the patient consent form (and assent form, as applicable per institutional standards) and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will submit reports of SAEs as outlined in Section 7.4.8. In addition, the Investigator agrees to submit progress reports to the IRB or IEC per their local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

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

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

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

9.1.3. Serious Breach of Protocol

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

9.1.4. Study Documentation, Confidentiality, and Records Retention

All documentation relating to the study should be retained for 2 years after the last approval in an ICH territory, or the period of time required by applicable local law, whichever is longer. If it becomes necessary for the Sponsor, the Sponsor's designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the Investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

The Investigator must ensure that the patients' confidentiality will be maintained. On the eCRFs or other documents submitted to the Sponsor or designees, patients should not be identified by their names, but by the assigned patient number or code. If patient names are included on copies of documents submitted to the Sponsor or designees, the names will be obliterated, and the assigned patient number or code added to the document. Documents not for submission to the Sponsor (eg, signed informed consent forms) should be maintained by the Investigator in strict confidence.

The Investigator must treat all of the information related to the study and the compiled data as confidential, whose use is for the purpose of conducting the study. The Sponsor must approve any transfer of information not directly involved in the study.

In compliance with local and/or regional regulations, this clinical study may be registered, and study results may be posted on public registries, such as ClinicalTrials.gov.

9.1.5. End of the Study

The end of the study is defined as the last patient last visit.

9.1.6. Discontinuation of the Clinical Study

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time. If the clinical study center does not recruit at a reasonable rate, the study may be discontinued at that clinical study center. Should the study be terminated and/or the clinical study center closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IEC/IRB and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Patients should then be withdrawn from the study.

9.2. Data Quality Control and Quality Assurance

9.2.1. Data Handling

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

9.2.2. Study Monitoring

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

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

9.2.3. Audits and Inspections

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

9.3. Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed manuscript must be provided and confirmed received at the Sponsor at least 30 days before its submission, and according to any additional publication details in the Investigator Agreement.

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11. APPENDICES

11.1. Pharmacokinetic Assessment Time Points

Table 5 contains a detailed schedule for the collection of blood and pooled urine samples for PK analysis.

Table 5 Pharmacokinetic Time Points

Study Visit	Time Point (hh:mm)	PK Blood	Pooled Urine Collection
Baseline (Day 1)	Predose (within 60 minutes before dosing)	X	
	00:00 (dose)		X (00:00-04:00)
	02:00 (±10 min)	X	
	04:00 (±10 min)		
	04:01 (±10 min)		X (04:01-08:00)
	08:00 (±15 min)	X	
	08:01 (±15 min)		X (08:01-24:00)
	24:00 (±30 min)	X	
Month 6 (Day 169)	Predose (within 60 minutes before dosing)	X	
	00:00 (dose)		X (00:00-04:00)
	02:00 (±10 min)	X	
	04:00 (±10 min)		
	04:01 (±10 min)		X (04:01-08:00)
	08:00 (±15 min)	X	
Month 12 (Day 337)	Predose (within 60 minutes before dosing)	X	
	00:00 (dose)		X (00:00-04:00)
	02:00 (±10 min)	X	
	04:00 (±10 min)		
	04:01 (±10 min)		X (04:01-08:00)
	08:00 (±15 min)	X	

11.2. Blood Volume Limits in Pediatric Patients

The maximum blood volume, which will be collected from pediatric patients over the course of the study, will be based on age and weight and will not exceed those specified in Table 6, which was adapted from the Human Subject Protection Program Guidance Document.

Table 6: Maximum Allowable Total Blood Volume Collection Chart

Body Weight	Body Weight	Total blood volume	Maximum allowable volume in a 24-hour period		Total volume collected in a 30-day period	
			2.5% of total blood volume	3% of total blood volume	5% of total blood volume	10% of total blood volume
(kg)	(lbs)	(mL)	(mL)	(mL)	(mL)	(mL)
1	2.2	100	2.5	3	5	10
2	4.4	200	5	6	10	20
3	6.6	240	6	7.2	12	24
4	8.8	320	8	9.6	16	32
5	11	400	10	12	20	40
6	13.2	480	12	14.4	24	48
7	15.4	560	14	16.8	28	56
8	17.6	640	16	19.2	32	64
9	19.8	720	18	21.6	36	72
10	22	800	20	24	40	80
11-15	24-33	880-1200	22-30	26.4-36	44-60	88-120
16-20	35-44	1280-1600	32-40	38.4-48	64-80	128-160
21-25	46-55	1680-2000	42-50	50.4-60	64-100	168-200
26-30	57-66	2080-2400	52-60	62.4-72	104-120	208-240
31-35	68-77	2480-2800	62-70	74 4-84	124-140	248-280
36-40	79-88	2880-3200	72-80	86.4-96	144-160	288-320
41-45	90-99	3280-3600	82-90	98.4-108	164-180	328-360
46-50	101-110	3680-4000	92-100	110 4-120	184-200	368-400
51-55	112-121	4080-4400	102-110	122.4-132	204-220	408-440
56-60	123-132	4480-4800	112-120	134.4-144	224-240	448-480
61-65	134-143	4880-5200	122-130	146 4-156	244-260	488-520
66-70	145-154	5280-5600	132-140	158.4-168	264-280	528-560
71-75	156-165	5680-6000	142-150	170.4-180	284-300	568-600
76-80	167-176	6080-6400	152-160	182.4-192	304-360	608-640
81-85	178-187	6480-6800	162-170	194.4-204	324-340	648-680
86-90	189-198	6880-7200	172-180	206.4-216	344-360	688-720
91-95	200-209	7280-7600	182-190	218.4-228	364-380	728-760
96-100	211-220	7680-8000	192-200	230 4-240	384-400	768-800

Adapted from http://www.feinsteininstitute.org/wp-content/uploads/2013/02/Maximum-Blood-Draw-Limits.pdf.[Feinstein Institute 2013]

ALN-GO1-002 PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES DATED 04 MAY 2020

A Phase 2, Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Administration of ALN-GO1 in Patients with Primary Hyperoxaluria Type 1

1. RATIONALE FOR PROTOCOL AMENDMENT

The primary purpose of this protocol amendment is to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter, dated 02 April 2020, to assure the safety of study participants while minimizing risks to study integrity amid the coronavirus 2019 (COVID-19) pandemic. These changes are in line with guidance from both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) on the conduct of clinical trials during the COVID-19 pandemic.[EMA 2020; FDA 2020] The USMs are summarized in Section 1.1.

This protocol amendment also incorporates changes that are not related to USMs. After ongoing review and assessment of the safety data from studies conducted with lumasiran, modifications are designed to enhance patient safety and reduce patient burden regarding blood sampling. These changes are summarized in Section 1.2 and will not be implemented until appropriate Health Authority and Ethics Committee (EC) and/or Institutional Review Board (IRB) approval.

1.1. Notification of Urgent Safety Measures Due to the Impact of the COVID-19 Pandemic

The USM modifications and new procedures are outlined below, and a detailed summary of the USMs is provided in Table 1. These measures were to be adopted immediately by the Investigator site as specified in the Dear Investigator Letter.

- **ALN-GO1 dosing outside the study center**

  Following appropriate training on ALN-GO1 administration, dosing will be permitted at a location other than the study center (eg, at home) by the patient/caregiver at all time points under the oversight of the Investigator and following consultation with the Medical Monitor. This measure is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to patients' homes for dosing.

  In order to assure uniform and comprehensive training and to assure compliance with the dosing instructions, the sponsor has prepared both Investigator and caregiver-facing written materials.

- **Assessment of adverse events and concomitant medications**

  In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess AEs and concomitant medication use.

- **Study visits**

Except for assessments with other specified timing requirements, study assessments and dosing can be performed within the expanded window of ±28 days (was ±7 days at Month 12 and ±14 days thereafter).

- **Renal ultrasound and electrocardiogram assessments**

  After Month 12, renal ultrasound and ECG assessments may be completed up to 9 months after the intended time point to ensure patient safety, and to the extent possible, maintain study integrity amid travel and other restrictions related to the COVID-19 pandemic.

  This expansion of the ECG assessment window is supported by results of a clinical corrected QT interval (QTc) assessment and nonclinical cardiac safety assessment of lumasiran, which demonstrated that lumasiran does not have QTc prolongation properties.

- **Assessments required to be performed in clinic**

  Where applicable country and local regulations and infrastructure allow for home healthcare, healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include pregnancy testing (as applicable), collection of blood and urine samples, measurement of vital signs, height and body weight, body system assessment, and preparation and administration of study drug (at the discretion of the Investigator) at all timepoints as specified in the Schedule of Assessments.

- **Full physical examination**

  If a visit is conducted offsite (eg, home), a body system assessment can be performed in lieu of a physical examination.

- **Impact of COVID-19 (collection of information)**

  Information related to the impact of the COVID-19 pandemic on patient participation in the study will be collected for each patient. Additional information regarding collection of this information, including completion of a new case report form specific to COVID-19, will be provided separately.

  This change is implemented to enable analysis of the impact of the COVID-19 global pandemic on clinical trial data.

- **Updates to study administration**

  Text was updated to provide clarification of Investigator responsibilities regarding communication of new study information to patients and IRB/IECs.

1.2. Changes Not Related to Urgent Safety Measures

The quality of life (QOL) questionnaire assessment data will not be summarized for this study as no predose data are available from Study ALN-GO1-001 Part B (Study 001B) to determine change from baseline. Additional changes to study conduct (outlined below) will not be implemented until appropriate HA and EC/IRB approval.

- Remove QOL as an exploratory objective and endpoint. The KDQOL for adults ≥18 years of age, and the PedsQL; the generic and the end-stage renal disease [ESRD] modules for children <18 years of age will not be collected after Month 12. QOL data will be listed only but not summarized. These assessments were not performed before the first lumasiran dose in Study 001B; therefore, change from baseline cannot be assessed.
- Clarify coagulation studies assessed in patients with elevated liver enzymes.
- Patients who discontinue pyridoxine (Vitamin B6) therapy during the study will not be required to provide additional blood samples for assessment of pyridoxine levels.
- Clarify assessment time points: performed predose only (ECGs), and at Months 24, 36, 48, and 54 after Month 12 (ECGs and renal ultrasound).

A detailed summary of changes is provided in Table 2. The following changes are not detailed: administrative changes, changes associated with administrative letters (between Amendments 1 and 2), and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting.

2. PROTOCOL AMENDMENT 2 DETAILED SUMMARY OF CHANGES

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

Table 1: Urgent Safety Measures COVID-19-related Changes to be Adopted Immediately

Purpose: Expand the use of offsite administration to include ALN-GO1 dosing by the caregiver and provide additional instructions on self administration, and preparation, handling, and storage of the study drug.

The primary change occurs in Section 6.2.2, Dose and Administration

Revised text: Study drug will be administered under the supervision of the Investigator or designee. **Dosing will be permitted at a location other than the study center (eg, the patient's home) by a healthcare professional with oversight of the Investigator at all time points, provided the patient has tolerated ALN-GO1 administered in the clinic.**

If the patient is unable to come to the study site, and a visit by a healthcare professional is not possible due to circumstances related to the COVID-19 pandemic, ALN-GO1 may be administered by the patient or the caregiver under the oversight of the Investigator, and following consultation with the Medical Monitor, as allowed by applicable country and local regulations. In such cases, the patient or caregiver must receive appropriate training on ALN-GO1 administration prior to dosing. Administration by a patient or caregiver is intended to remain in effect only during periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site and healthcare professionals to go to the patients' homes for dosing.

In addition, instructions and procedures related to administration of ALN-GO1 by a patient or caregiver will be provided in the Patient/Caregiver Storage and Administration Instructions.

Section(s) also reflecting this change:

- Section 6.2.4, Preparation, Handling, Storage

Purpose: Allow additional offsite assessments

The primary change occurs in Section 7, Study Assessments.

Revised text: **Where applicable country and local regulations and infrastructure allow for home healthcare**, healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include pregnancy testing (as applicable), collection of blood and urine samples, measurement of vital signs, **height and body weight**, **body system assessment**,

and preparation and administration of study drug (at the discretion of the Investigator) at all timepoints **as specified in the Schedule of Assessments**.

Section(s) also reflecting this change:

- Section 7.4.3, Physical Examination
- Section 7.4.7.2, Pregnancy Testing

Purpose: Expand the study visit window.

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

Revised text: The study site visit window was changed from ±~~14~~ days to ±**28** days through the end of the study.

Purpose: Expand the window for body weight measurement.

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

Revised text: **Body weight must be obtained within 4 months prior to dosing.**

Section(s) also reflecting this change:

- Section 6.2.2, Dose and Administration

Purpose: Expand study assessment windows for ECGs and renal ultrasound.

The primary change occurs in Section 7.4.4, Electrocardiogram

Revised (added) text: **During periods of time when the COVID-19 pandemic impedes the ability of patients to travel to the study site, ECGs may be completed up to 9 months after the intended timepoint.**

Section(s) also reflecting this change:

- Section 7.4.6, Renal Ultrasound

Purpose: Allow continual assessments of AEs and concomitant medications via remote contact.

The primary change occurs in Table 1, Schedule of Assessments (notes)

Revised (added) text: • **In situations where a study visit is unable to be completed (either at the site or offsite by a healthcare professional), the Investigator (or delegate) will verbally contact the patient within the study visit window to assess concomitant medications and adverse events.**

Purpose: Collect information related to the impact of the COVID-19 pandemic on patient participation in the study.

The primary change occurs in Section 7.4.9, COVID-19 Data Collection

Revised text: **Information on the coronavirus disease 2019 (COVID-19) infection status of the patient, if known, and other information on the impact of the COVID-19 pandemic on the patient's participation in the study will be collected.**

Section(s) also reflecting this change:

- Section 8.2, Statistical Methodology

Purpose: Revise and update informed consent instructions.

The primary change occurs in Section 9.1.1, Informed Consent

Revised (added) text: **The Investigator will inform the patient/legal guardian if new information becomes available that may be relevant to the patient's/legal guardian's willingness to continue participation in the study. Communication of this information should be documented**.

Purpose: Revise and update ethical review instructions.

The primary change occurs in Section 9.1.2, Ethical Review

Revised (added) text: In addition, the IRB or IEC must approve all advertising used to recruit patients for the study (**except those that support the need to remove an apparent immediate hazard to the patient**).

Table 2: Changes Not Related to Urgent Safety Measures to be Implemented After Health Authority and Ethics Committee(EC)/Institutional Review Board (IRB) Approval, where applicable

Purpose: Remove QOL as an exploratory study objective and stop collection of the QOL (KDQOL and PedsQL) questionnaires after Month 12.

The primary change occurs in Section 2.3, Exploratory Objectives

- ~~Characterize quality of life~~

Sections also reflecting this change:

- Section 3.3, Exploratory Endpoints
- Section 7.5.1, Quality of Life
- Section 8.2.9, Other Analyses
- Synopsis, Exploratory Objectives; Exploratory Endpoints
- Table 1, Schedule of Assessments

Purpose: To clarify coagulation parameters.

The primary change occurs in Section 6.2.3, Table 2, Monitoring and Dosing Rules for Asymptomatic Patients with Confirmed Isolated Elevations of ALT and/or AST >3 x ULN, with no Alternative Cause

Revised text: • Hematology, serum chemistry, **and** LFT~~, and coagulation~~ per Table 3

- **Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio)**

Section(s) also reflecting this change:

- Section 7.4.7.3, Additional Liver Function Assessments

Purpose: Remove the requirement for measurement of pyridoxine after discontinuation of pyridoxine therapy.

The primary change occurs in Section 6.3, Concomitant Medications**.**

Revised (deleted) text: ~~If pyridoxine therapy is discontinued, pyridoxine levels should be assessed for at least the next 2 study visits.~~

Section(s) also reflecting this change:

- Table 1, Schedule of Assessments

Purpose: Clarify the timing of 12-lead ECGs and renal ultrasounds.

The primary change occurs in Table 1, Schedule of Assessments

Revised text: After Month 12, ECGs and renal ultrasounds will be performed at ~~X (Q12M)~~ **Months 24, 36, 48, and 54 only**.

Section(s) also reflecting this change:

- Section 7.4.4, Electrocardiogram (remove the 2 to 4 hours after dosing timepoint)

Purpose: Clarify that vital signs will be measured in the supine or seated position.

The primary change occurs in Section 7.4.1, Vital Signs

Revised text: Vital signs will be measured in the supine **or seated** position, after the patient has rested comfortably for approximately 10 minutes.

3. REFERENCES

EMA (Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 1.0 (20/03/2020). https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic)

US FDA (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. (27 March 2020) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic).