Official Title:	**A Phase 1/2, Single-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Safety, Tolerability, Pharmacokinetic and Pharmacodynamics Study of Subcutaneously Administered ALN-GO1 in Healthy Adult Subjects, and Patients With Primary Hyperoxaluria Type 1**
NCT Number:	**NCT02706886**
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STATISTICAL ANALYSIS PLAN (SAP)

A Phase 1/2, Single-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-GO1 in Healthy Adult Subjects, and Patients with Primary Hyperoxaluria Type 1

Investigational Product:	ALN-GO1
Protocol Number:	ALN-GO1-001
Development Phase:	1/2
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Tel: 1-617-551-8200
Protocol Version Number and Date:	Original Protocol, 18 December 2015 Amendment 1, 01 July 2016 Amendment 2, 21 September 2016 Amendment 3, 09 December 2016 Amendment 4, 27 June 2017
SAP Version:	Original
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Confidentiality Statement

A Phase 1/2, Single-Blind, Placebo-Controlled, Single- and Multiple-Ascending Dose Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-GO1 in Healthy Adult Subjects, and Patients with Primary Hyperoxaluria Type 1

Protocol Number:	ALN-GO1-001
Original Protocol:	18 December 2015
Amendment 1	01 July 2016
Amendment 2	21 September 2016
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SAP Version:	Original, 1 November 2017

This Statistical Analysis Plan has been reviewed and approved by:

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Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AUC	area under curve
BMI	body mass index
BUN	blood urea nitrogen
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
HLT	high level term
ICF	informed consent form
ICH	International Conference on Harmonization
LLOQ	lower level of quantitation
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	modification of diet in renal disease
NQ	non-quantifiable
PD	pharmacodynamics
PH1	Primary Hyperoxaluria Type 1
PK	Pharmacokinetics
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
SAD	single-ascending dose
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCR	serum creatinine
SD	standard deviation
SE	standard error
SAE	serious adverse advent
SAP	statistical analysis plan
SOC	system organ class
SRC	safety review committee
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and analysis to be performed based on Alnylam Pharmaceuticals, Inc., Protocol ALN-GO1-001 (Original, 18 December 2015; Amendment 1, 01 July 2016; Amendment 2, 21 September 2016; Amendment 3, 09 December 2016; and Amendment 4, 27 June 2017). Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective

- Evaluate the safety and tolerability of single- and multiple-ascending doses of ALN-GO1, respectively, in healthy adult subjects and in patients with Primary hyperoxaluria type 1 (PH1)

2.2 Secondary Objectives

- Characterize the pharmacokinetics (PK) of ALN-GO1
- Evaluate the pharmacodynamics (PD) of ALN-GO1

2.3 Exploratory Objectives

- [redacted]
- [redacted]

3 STUDY OVERVIEW

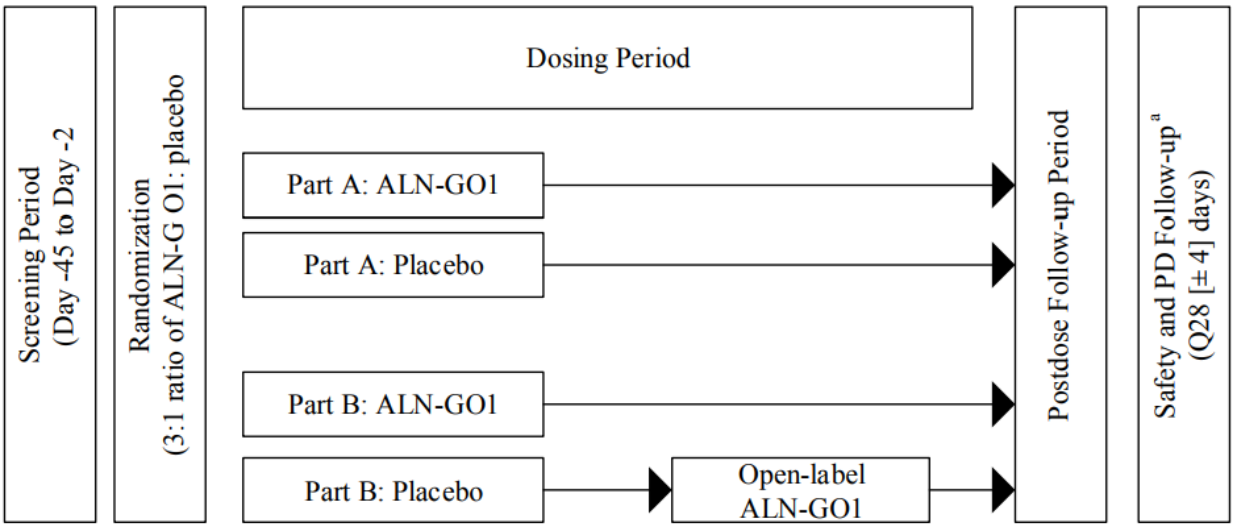
3.1 Summary of Study Design

This is a randomized, single-blind, placebo-controlled study of subcutaneously administered ALN-GO1. The study is designed to evaluate the safety, tolerability, PK, and PD of single- and multiple-ascending doses of ALN-GO1 and will be conducted in 2 parts:

- Part A: single-ascending dose (SAD) part in healthy adult subjects, followed by
- Part B: multiple-ascending dose (MAD) part in adult and pediatric patients with PH1

The study will be conducted in a single-blind manner, with the Investigators, SRC, and Sponsor unblinded to permit ongoing unblinded review of safety, tolerability, PK, and PD data.
Part A will be conducted at 1 clinical study center in the UK. Part B is expected to take place at approximately 12 clinical study centers worldwide.
The study design is summarized in Figure 1.

Figure 1: Study Design



[a] Patients in Part B will be invited to participate in an open-label extension study provided they meet the criteria described in Protocol ALN-GO1-001 Section 4.1.2 (Amendment 4; 27 June 2017).

3.1.1 Single-ascending Dose Part in Healthy Adult Subjects (Part A)

Part A is the single-ascending dose part of the study in healthy adult subjects. Subjects will be enrolled in 1 of 3 ascending dose cohorts, with the possibility for 2 additional optional cohorts. Each cohort will be comprised of 8 subjects randomized 3:1 to ALN-GO1 or placebo (study drug).

Subjects will be screened from -45 to -2 days before study drug administration. Subjects will be admitted to the clinical study center on Day -1 to determine continued eligibility and for predose assessments. Subjects in each cohort will be randomized on Day 1 and will receive 1 SC dose of study drug. Subjects will be discharged from the clinical study center on Day 2 after completing the 24-hour postdose follow-up assessments.

Subjects will return to the clinical study center on an outpatient basis for safety, tolerability, PK, and PD monitoring at time points specified in the Schedule of Assessments through the last postdose follow-up visit (Day 57). Safety and PD follow-up will continue: 1) for at least 57 days, and 2) until plasma glycolate decreases to a level that is no more than 20% above of baseline or until plasma glycolate is below the upper limit of normal (≤14 nmol/mL).

3.1.2 Multiple-ascending Dose Part in Patients with Primary Hyperoxaluria Type 1 (Part B)

Part B is the multiple-ascending dose part of the study in up to 24 adult and pediatric patients with PH1 with relatively well-preserved renal function. The overall allowable age range of the patients in Part B will be 6-64 years.

Two mandatory ascending dose cohorts will be enrolled, with the possibility to also enroll up to 3 additional optional cohorts to further explore the optimal dose or regimen. Each cohort will be comprised of 4 patients, randomized 3:1 to ALN-GO1 or placebo. Up to 2 cohorts in Part B may be expanded by up to 4 additional patients (these patients will all receive ALN-GO1, not placebo).

Patients will be screened within 45 days prior to study drug administration. Baseline urinary oxalate excretion and creatinine clearance will be assessed through 24-hour urine collections. Patients will be randomized between Day -1 and Day 1 and will receive the first dose of ALN-GO1 or placebo on Day 1. The 24- and 48-hour postdose follow up assessments will take place on Day 2 and Day 3. Patients who receive study drug monthly will return to the clinical study center for safety, tolerability, PK, and PD monitoring at time points specified in the Schedule of Assessments (Protocol ALN-GO1-001 Table 2; Amendment 4, 27 June 2017) for the remaining 2 single-blind doses of study drug (through Day 57). After completion of the blinded portion of the study, patients dosed monthly will be unblinded (on or after Day 78). Patients who initially received placebo will then receive ALN-GO1 at the same dose administered to the cohort into which they were initially randomized and will follow the assessment schedule as indicated (Protocol ALN-GO1-001 Table 3; Amendment 4, 27 June 2017).

After the dosing period, patients will return to the clinical study center for continued safety, tolerability, PK, and PD monitoring through the last postdose follow-up visit. Following completion of the postdose follow-up period, patients will be invited to participate in an open-label extension study provided that:

- Urinary oxalate is above the ULN and patients meet at least 1 of the following criteria:
    - One 24-hour urinary oxalate value is >80% of baseline.
    - Two 24-hour urinary oxalate values are above the midpoint between their baseline and nadir 24-hour urinary oxalate values. The nadir must be from a valid collection after all doses are administered.
    - At least 12 months have elapsed from time of final dose administration.

For patients who do not enroll in the open-label extension study, safety and PD follow up will continue until:

- 24-hour urinary oxalate is >80% of baseline, AND
- Plasma glycolate is <20% above baseline or ≤ the ULN

3.2 Study Assessments

The complete Schedule of Assessments is found in Table 1 (Single-ascending Dose Cohorts in Healthy Subjects (Part A)), Table 2 (Multiple-ascending Dose Cohorts in Patients with Primary Hyperoxaluria Type 1 (Part B – Monthly Dosing)), Table 3 (Multiple-ascending Dose Cohorts in Patients with Primary Hyperoxaluria Type 1 (Part B) who Previously Received Placebo and will Receive Open-Label ALN-GO1 – Monthly Dosing), and Table 4 (Multiple-ascending Dose

Cohorts in Patients with Primary Hyperoxaluria Type 1 (Part B – Quarterly Dosing)) of Protocol ALN-GO1-001 (Amendment 4; 27 June 2017).

3.3 Duration of Treatment and Overall Duration of Study

The duration of the study is as follows:

- Part A: The estimated total time on study, inclusive of screening, for each subject is up to 405 days. The duration of treatment is a single dose.
- Part B:
    - For patients dosed monthly: The duration of treatment for patients initially randomized to receive active study drug is 57 days. The estimated total time on study, inclusive of screening, for each patient is up to 462 days. Additionally, the duration of treatment for patients initially randomized to receive placebo is 141 days. The estimated total time on study, inclusive of screening, for each patient initially randomized to receive placebo, then active study drug, is up to 546 days.
    - For patients dosed quarterly: The duration of treatment is 85 days for patients randomized to placebo and active study drug. The estimated total time on study, inclusive of screening, is up to 490 days.

The overall duration of the study is estimated to be 4 years, including enrollment.

3.4 Study Populations

In Part A, the study population will consist of healthy adult volunteers ages 18 years and older.

In Part B, the study population will consist of pediatric and adult patients (ages 6 years - 64 years inclusive) that have a confirmed diagnosis of PH1.

Additional information regarding specific inclusion and exclusion criteria are listed in Protocol ALN-GO1-001 Section 5.1 and 5.2 (Amendment 4; 27 June 2017).

3.5 Study Centers

The single-ascending dose (SAD) part in healthy adult subjects (Part A) will be conducted at 1 clinical study center in the United Kingdom. The multiple-ascending dose (MAD) part in patients with PH1 (Part B) is expected to take place at approximately 12 clinical study centers worldwide.

3.6 Randomization and Blinding

This is a randomized, single blind, placebo-controlled study; therefore, only the study subjects/patients will be blinded to treatment assignment. In Parts A and B, after confirmation of eligibility, during screening, and upon admission the clinical study center, subjects/patients will

be assigned to a dose cohort and randomized in a 3:1 ratio (ALN-GO1:placebo). No subject/patient will be a member of more than 1 cohort. A unique subject/patient identification number, incorporating the clinical study center number, will be assigned sequentially to the subject/patient.

The clinical study center pharmacy staff will randomize the subject/patient in accordance to a cohort-specific randomization list generated by the biostatistician at the Contract Research Organization (CRO) for appropriate dispensation of the study drug.

Patients in Part B dosed monthly will be unblinded on or after Day 78 in order for patients and their families to be better prepared for the transition to receive ALN-GO1 if initially randomized to placebo. Patients dosed quarterly will be unblinded to initial treatment assignment following completion of the postdose follow-up period. The Investigators, Medical Monitors at the Sponsor and CRO, clinical study center personnel, pharmacokineticist, and members of the SRC will have knowledge of the treatment assignment. The clinical study center pharmacy staff will maintain the single-blind according to clinical study center-specific procedures and the Pharmacy Manual. Syringes containing dispensed study drug will be masked in the pharmacy before transfer to the clinic.

During the blinded period, if the subject/patient becomes seriously ill during the study, and the treating physician determines that the clinical management of the subject requires that the subject know the study drug assignment, the Investigator may break the blind, as necessary.

Based on SRC review of accumulated safety, tolerability, and PD data, 3 additional cohorts may be enrolled and dosed according to the same eligibility criteria in Part B to better define safety or PD effects. Additional cohorts may be enrolled at higher, lower, or intermediate dose levels, but will not exceed the maximum administered dose of 6 mg/kg, and will follow the protocol-specified dose escalation criteria.

Based on SRC review of accumulated safety, tolerability, and available PD data, up to 2 cohorts in Part B may be extended by up to 4 additional patients based on study progression and stopping rules. These patients will all receive active drug, not placebo.

4 STATISTICAL METHODOLOGY

Unless stated otherwise, the methodology described in this section will apply to both Part A and Part B of this study. Data from Part A and Part B will be analyzed separately.

Summary analyses will be presented as follows. The primary analyses will be presented in order of ascending ALN-GO1 dose with the placebo group presented first. Patients randomized to placebo will be pooled across enrollment cohorts for all analyses where applicable.

4.1 Sample Size Determination

The sample size was determined on the basis of clinical considerations rather than power calculations. Up to a total of 64 participants (40 subjects in Part A, 24 patients in Part B) are planned to be enrolled in this study, including optional and expansion cohorts.

4.2 Analysis Populations

The following analysis populations will be considered for the purposes of data analysis.

4.2.1 Safety Analysis Set

For both Part A and Part B, the Safety Analysis Set will include all subjects who received at least 1 dose of study drug (placebo or ALN-GO1).

The Safety Analysis Set will be used for safety analyses. Subjects will be summarized according to the treatment actually administered.

4.2.2 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects/patients who receive at least 1 dose of study drug and have at least 1 postdose sample for PK parameters and who have evaluable PK data.

The PK analysis will be based on the PK Analysis Set.

4.2.3 Pharmacodynamic Analysis Set

The PD Analysis Set will include all subjects/patients who receive at least 1 dose of study drug and who have at least 1 postdose blood and/or urine sample evaluable for PD parameters.

PD summaries will be based on the PD Analysis Set.

4.3 General Statistical Considerations

The primary goal of the study is to evaluate the safety and tolerability of ALN-GO1 in healthy adult subjects and patients diagnosed with PH1. The data cutoff date for the primary analysis will occur after all subjects have either discontinued the study or completed all safety follow-up assessments (as in Section 3.2).

Continuous data will be described using descriptive statistics including the number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical and ordinal data will be described using the subject/patient count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, and standard deviation will be displayed to one level of precision greater than the data collected. Summary tables will present results by cohort for each ALN-GO1 dose in ascending dose order, total (all subjects receiving ALN-GO1), and placebo, where the placebo subjects/patients will be

combined across dose cohorts. Data will be displayed in all listings sorted by study part and cohorts with placebo ordered last.

Subjects/patients will be identified in the listings by the subject/patient identification number concatenated with the investigator number.

When count data are presented, the percentage will not be presented when the count is zero in order to draw attention to non-zero counts. A row denoted "Missing" will be included in tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of non-missing values in that cohort/treatment, unless otherwise specified.

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

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

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

Study day = Date of assessment – date of first study drug dose.

4.3.1 Baseline Definition

The baseline value is defined as the last non-missing value before the first dose of the randomized study drug, unless otherwise specified.

In Part B, for patients who are randomized initially to placebo, the baseline value for the placebo dosing period is defined as the last non-missing value before the first dose of placebo. For these patients, their baseline value for the open-label ALN-GO1 period is defined as the last non-missing value before the first dose of ALN-GO1.

4.3.2 Multicenter Studies

Part A will take place at a single study center.

Part B will take place at multiple centers but the center effect will not be considered for the planned descriptive analysis. Data will not be stratified by study center for reporting of descriptive statistics.

4.3.3 Multiple Comparisons

No adjustments for multiple comparisons will be made for the planned descriptive analysis.

4.3.4 Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. non-missing) data values will be used for reporting of descriptive statistics unless otherwise stated.

4.3.5 Examination of Subgroups

No subgroup-specific analysis is planned.

4.3.6 Interim Analysis

No formal interim statistical analysis is planned for this study. The Safety Review Committee (SRC) will perform ongoing reviews of safety, tolerability, and available PD data, with the primary purpose of protecting the safety of subjects/patients participating in this clinical study.

5 STUDY ENDPOINTS

Primary Endpoint

- The primary endpoint is the incidence of adverse events (AEs). Safety will also be evaluated through vital signs, electrocardiograms (ECGs), clinical laboratory assessments, and physical examinations.

Secondary Endpoints

For Part A, the secondary endpoints are:

- PK parameters including, but not limited to, maximum plasma concentration [C_{max}], time to reach maximum plasma concentration [t_{max}], area under the plasma concentration versus time curve [AUC], apparent terminal elimination half-life [$t_{½}$], fraction eliminated in urine [fe/F], and renal clearance [CL_R]
- Plasma and urine glycolate concentration

For Part B, the secondary endpoints are:

- First dose and steady state PK parameters including, but not limited to, C_{max}, t_{max}, AUC, $t_{½}$, fe/F, and CL_R
- Urinary oxalate excretion (oxalate content in 24-hour urine collection)
- Urinary glycolate excretion (glycolate content in 24-hour urine collection)
- Plasma glycolate concentration
- Calculated creatinine clearance

Exploratory Endpoints

The exploratory endpoints are:

- Plasma oxalate concentration
- [redacted]

Additional exploratory endpoints for Part B only are:

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

6 STUDY ASSESSMENTS

For both Part A and Part B, the assessments described in this section will be collected at assessment times throughout the course of the study. The exact frequency and timing of collection may be found in the Schedule of Assessments in Protocol ALN-GO1-001 (Amendment 4; 27 June 2017) for Safety and PD variables: Table 1 for Part A; Tables 2 and 3 for Part B monthly dosing, and Table 4 for Part B quarterly dosing. A detailed schedule of time points for the collection of blood and urine samples for PK analysis is in Protocol ALN-GO1-001 (Amendment 4; 27 June 2017) Table 10 for Part A and in Tables 11 and 12 for Part B. Detailed assessments will not be repeated in this document and it will be referred to herein as the Schedule of Assessments.

6.1 Safety Assessments

6.1.1 Adverse Events

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. AEs will be graded according to the CTCAE criteria (Version 4.0 or higher). Refer to CTCAE for unique clinical descriptions and additional information regarding grading of severity for specific AEs.

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 AE is stable, as appropriate.

6.1.2 Vital Signs

Vital sign measurements include:

- Systolic and diastolic blood pressure (mmHg)
- Heart rate/Pulse rate (beats/min)

- Body temperature (ºC)
- Respiratory rate (breaths/min)

6.1.3 Weight and Height

For all participants, height will be measured in centimeters. For Part B patients who are <18 years, height will be measured in triplicate and the mean value will be used to calculate the estimated glomerular filtration rate (eGFR) using the Schwartz Bedside Formula.

The variables recorded will include:

- Height (centimeters)
- Weight (kilograms)
- Body Mass Index (BMI) (kg/m^2) which will be calculated from the height and weight measurement.

The baseline value for height for subjects in Part A and patients in Part B who are 18 years and older is defined as the last non-missing value before first dose of study drug; and for patients in Part B who are younger than 18 years old is defined as the mean of the last triplicate before first dose of study drug.

6.1.4 Physical Examinations

A full physical examination or a symptom-directed physical examination will be performed at selected time points, as described in the Schedule of Assessments.

A symptom-directed physical examination will include the evaluation of changes in symptoms or onset of new symptoms since the last visit.

6.1.5 Electrocardiograms (ECGs)

For both parts A and B, triplicate 12-lead ECGs will be measured 5 minutes apart at times indicated in the Schedule of Assessments. Recording will be obtained after the subject has rested comfortably in the supine position for approximately 10 minutes. ECGs should be performed at approximately the same time of day throughout the study. The Investigator (or designee) is responsible for reviewing ECGs and to determine the clinical significance of the results. The overall interpretation of the ECG will be recorded and any abnormality specified. The Investigator will provide a determination regarding the change from baseline ECG and specification of the change. The electrophysiological parameters assessed will include

- Rhythm
- Ventricular rate
- PR interval

- QRS duration
- QT interval
- ST and T waves
- Bazett-corrected QT interval (QTcB)
- Fridericia-corrected QT interval (QTcF)

All triplicate ECG measurements at a particular time point will be averaged prior to analysis and summarization.

6.1.6 Echocardiograms (Part B Only)

ECHO assessments will be performed according to instructions provided in a study manual at select time points outlined in the Schedule of Assessments. The Investigator or designee is responsible for reviewing the ECHOs to assess whether the results have changed since the Screening/Baseline visit and to determine the clinical significance of the results.

6.1.7 Clinical Laboratory Assessments

For both Part A and Part B, clinical laboratory tests will be evaluated at the times indicated in the Schedule of Assessments. Laboratory tests to be collected include:

- Hematology: Complete blood count with differential
- Serum Chemistry: Sodium, blood urea nitrogen (BUN), Creatinine and estimated glomerular filtration rate (eGFR) calculation (using the modification of diet in renal disease or Schwartz formula depending on age), uric acid, total protein, glucose, potassium, phosphate, albumin, calcium, carbon dioxide/bicarbonate, chloride
- Cardiac Enzyme: Troponin I
- Liver Function Tests: aspartate transaminase (AST), alkaline phosphatase (ALT), alkaline phosphatase (ALP), total and direct bilirubin
- Coagulation Panel: Prothrombin Time, Activated partial thromboplastin time, International Normalized Ratio
- Urinalysis: Visual inspection of appearance and color, pH (dipstick), specific gravity, Ketones, Albumin (optional), Glucose, Protein, Bilirubin, Nitrite, RBCs, Urobilinogen, Leukocytes, Microscopy (if clinically indicated)
- Immunogenicity: Anti-drug antibodies
- Pregnancy Testing: β-human chorionic gonadotropin (women of child bearing potential only). Serum testing will be performed at screening or menarche, and urinary screening thereafter.

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

MDRD Formula

- Conventional units:

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

- SI units

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

Schwartz Bedside Formula

- Conventional units:

  eGFR (mL/min/1.73m^2) = (.413 × height [cm])/ S_{Cr} (mg/dL)

- SI units:

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

All triplicate height measurements at a particular time point will be averaged and the mean will be used in the calculation of the eGFR.

6.1.8 Other Safety Variables

In Part A and Part B, testing for drugs of abuse will be conducted and judged at screening for participants ≥18 years of age.

6.2 Pharmacokinetics Assessments

6.2.1 Sample Collections for Pharmacokinetic Analysis

Blood and urine samples will be collected for PK analysis at scheduled time points listed in Protocol ALN-GO1-001 (Amendment 4; 27 June 2017) Table 10 for Part A and in Table 11 and Table 12 for Part B.

6.2.2 PK Parameters

In Part A, PK parameters following single dose of ALN-GO1 (Day 1) will be characterized. In Part B, PK parameters following single and multiple doses (Day 1 and Day 57 for monthly dosing cohorts; Day 1 and Day 85 for quarterly dose cohorts) of ALN-GO1 will be calculated.

The following PK parameters will be calculated from the individual plasma concentration profiles ALN-GO1 by standard non-compartmental methods:

Parameters	Units	Description
C_{max}	ng/mL	Maximum observed plasma concentration
t_{max}	h	The time to reach the maximum observed concentration
AUC_{0-24}	ng·h/mL	The area under the plasma concentration versus time curve, from time 0 to the 24 hour concentration (C_{24h}), as calculated by the linear trapezoidal method
AUC_{0-last}	ng·h/mL	The area under the plasma concentration versus time curve, from time 0 to t_{last} (time of last quantifiable concentration) as calculated by the linear trapezoidal method.
AUC_{0-inf}	ng·h/mL	The area under the plasma concentration versus time curve, from time 0 extrapolated to infinity, calculated as: $AUC_{0-inf} = AUC_{0-last} + C_{last}/\lambda z$ (Reported for Part A only)
$AUC_{tau,ss}$	ng·h/mL	Steady state area under the plasma concentration versus time curve, over the dosing interval at steady state (Reported for Part B only)
Lambda z (λ_Z)	h^{-1}	Apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
$t_{½}$	h	Apparent terminal elimination half-life, calculated as: $ln(2)/\lambda_Z$
CL/F	L/h	Total apparent body clearance after extravascular administration, calculated as: $Dose/AUC_{0-inf}$
CL/Fss	L/h	Total apparent body clearance at steady-state after extravascular administration, calculated as: $Dose/AUC_{0-tau}$ (Reported for Part A only)
V_Z/F	L	Apparent volume of distribution based on the terminal elimination phase, calculated as: $Dose/(AUC_{0-inf} \times \lambda_Z)$ (for Part A) or $Dose/(AUC_{0-tau} \times \lambda_Z)$ (for Part B)

The following urine PK parameters will also be calculated:

Parameters	Units	Description
$A_{e(0-24)}$	mg	Cumulative amount of drug excreted in urine after dosing, calculated as the sum of ($C_{ur} \times V_{ur}$), where C_{ur} is the concentration in urine and V_{ur} is the volume of urine collected.
f_e/F	%	Fraction eliminated in the urine, calculated as $(A_{e(0-24)}/Dose) \times 100$
CL_R	L/h	Renal clearance, calculated as $A_{e(0-24)}/AUC_{0-24}$

In addition, Part B samples may also be used to characterize the [redacted].

6.2.3 Pharmacokinetic Parameter Calculation

Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The PK parameters λ_z, $t_{½}$, $AUC_{0\text{-}inf}$, CL/F, and V_z/F will not be presented for those subjects who do not exhibit a terminal elimination phase in their concentration versus time profiles. In order to estimate the apparent first-order terminal elimination rate constant, λ_z, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λ_z. The constant λ_z will not be assigned if:

- The terminal elimination rate constant indicates a positive slope ($\lambda_z < 0$)
- T_{max} is one of the last 3 data points
- The adjusted regression coefficient (R^2) is less than 0.8
- $t_{1/2}$ is more than half the total sampling interval

In cases where the λ_z interval is not assigned, the values of the associated parameters (λ_z, $t_{½}$, $AUC_{0\text{-}inf}$, CL/F, V_z/F, and possibly $AUC_{0\text{-}24h}$) will not be reported.

The linear trapezoidal method will be used in the computation of all AUC values. $AUC_{0\text{-}inf}$ will be calculated as $AUC_{0\text{-}last} + C_{last,observed}/\lambda_z$, where $C_{last,observed}$ is the last observed evaluable plasma concentration.

6.2.4 Handling of Missing or Non-Quantifiable PK Data

For the calculation of individual pharmacokinetic profiles, missing or non-quantifiable (NQ) data will be handled based on the current knowledge of drug pharmacokinetics measures. The methods for missing data imputation will be as follows:

- Missing values will generally be omitted (set to missing) in the derivation of PK parameters and from the individual subject plots.
- A non-quantifiable (NQ) value, and all subsequent NQ values before the first measurable concentration will be set to zero in the derivation of PK parameters, statistical analyses, and the individual subject plots.
- If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of PK parameters, statistical analysis, and the individual subject plots.
- NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of PK parameters, statistical analysis, and from the individual subject plots.

For linear plots, zero concentration value(s) before the first measurable concentration will be included in the plot. For log-linear plots, zero concentration value(s) before the first measurable concentration will be assigned a missing value. Concentration values that are less than lower limit of quantitation (LLOQ) will be indicated on appropriate listings without imputation.

For urine PK parameters, if urine concentration values or volumes are missing, $A_{e(0-24)}$, f_e, and CL_R will not be estimated and will be listed as NA.

6.3 Pharmacodynamics 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 for Part A and Part B.

In Part B, 24-hour urine collections will be analyzed for glycolate, oxalate, and creatinine excretion. The 24-hour urine collection starting on Day -1 must conclude on Day 1 before administration of the first dose of study drug. PD blood samples will also be collected prior to dosing for the analysis of plasma glycolate and oxalate concentration.

For Part A, baseline for PD parameters is defined as the last non-missing measurement prior to the first dose of randomized study drug.

For Part B, baseline is defined as the median for 24-hour urine PD parameters of the measurements and as the mean for all other PD parameters of the measurements during the screening period prior to the first dose date/time of study drug in the study. Patients randomized to placebo will receive open-label ALN-GO1 after their single-blind placebo dosing period. Baseline for the open-label ALN-GO1 dosing period for these patients will be the median or mean of all assessments after the single-blind placebo first dose date/time and prior to the open-label ALN-GO1 first dose date/time for 24-hour urine PD parameters or all other PD parameters, respectively.

The following PD parameters will be assessed in Part A:

- Plasma glycolate concentration
- Urine glycolate concentration
- [redacted]
- [redacted]

The following PD parameters will be assessed in Part B:

- Plasma glycolate concentration
- Urine glycolate concentration
- Plasma oxalate concentration

- Urine oxalate concentration
- 24-hour urine oxalate content corrected for BSA
- 24-hour urine creatinine content
- 24-hour urine oxalate/creatinine ratio
- 24-hour urine glycolate content

6.4 Exploratory Assessments

[redacted]

[redacted]

[redacted]:

- [redacted]
- [redacted]

[redacted]:

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

6.5 Immunogenicity

Blood samples will be collected to evaluate antidrug antibodies (ADA). Blood samples for ADA testing that are collected on the day of dosing must be collected before study drug administration. Blood samples to evaluate ADAs will be collected throughout the treatment and follow-up periods as detailed in the Schedule of Assessment. Confirmed positive ADA samples will be tested for cross-reactivity with DNA and nucleic acids.

7 STATISTICAL ANALYSIS

This study is designed to evaluate the safety, tolerability, PK, and PD of single- and multiple-ascending doses of ALN-GO1. The described analyses will be carried out separately for Part A and Part B of this study.

Statistical analyses will be primarily descriptive and no formal hypothesis testing will be performed in this study. Assessments of change from baseline to post-treatment will be computed only for those subjects with both baseline and post-treatment measurements.

7.1 Analysis Periods in Part A

Part A is the single ascending dose study part. Subjects will be randomized in a 3:1 ratio (ALN-GO1: placebo) to receive 1 dose of a single-blind study drug and followed until Day 57/End of Treatment (EOT). If additional follow-up beyond Day 57 (End of Treatment) is required, this will be defined as the safety and PD follow-up period.

In Part A, summary statistics for Safety and PD data will be presented by ascending dose level of ALN-GO1 and the pooled placebo group with pooled placebo presented first. The pooled placebo group includes subjects receiving placebo across all cohorts.

7.2 Analysis Periods and By-visit Data Presentation in Part B

Part B is the multiple ascending dose study part including monthly and quarterly dosing regimens with ALN-GO1 or placebo. Analysis periods and treatment groups will be defined in Section 7.2.1 and Section 7.2.2.

All data listings will be presented with corresponding treatment, study day relative to first dose date of study drug, and study day relative to first dose of ALN-GO1.

7.2.1 Single-Blind Dosing Period

In Part B, Safety and PD data during the single-blind period will be summarized for the period starting from the first single-blind study drug date/time up to, and including, Study Day 85 for patients randomized to ALN-GO1, or prior to the first dose of ALN-GO1 for patients randomized to placebo. Patients receiving placebo in all regimen and dose cohorts will be pooled together.

7.2.2 ALN-GO1 Dosing Period and Follow-up Periods

In monthly dosing regimen cohorts, after receiving 3 single-blind doses of study drug (and completing the corresponding assessments in the Schedule of Assessments), patients initially randomized to placebo will be unblinded and administered 3 doses of active ALN-GO1 (at the dose level of the cohort) in an open-label manner and will follow a parallel assessment schedule, as in the Schedule of Assessments (Protocol ALN-GO1-001 Table 3; Amendment 4, 27 June 2017).

In quarterly dosing regimen cohorts, after the single-blind dosing period, all patients will receive an open-label dose of ALN-GO1 (at the dose level of the cohort) following the Schedule of Assessments (Protocol ALN-GO1-001 Table 4; Amendment 4, 27 June 2017).

Safety and PD data collected during the ALN-GO1 open-label period from these patients who received placebo initially will be realigned in terms of Study Day on ALN-GO1with data collected during the single-blind period from patients who were initially randomized to ALN-GO1. This data may be used for a separate Safety and PD analysis through Day 85 relative to ALN-GO1 dosing, inclusive.

The Study Day relative to the first dose of ALN-GO1 will be defined as:

- Study Day relative to the first dose of ALN-GO1= Date of assessment – Date of first dose of ALN-GO1 + 1.

The ALN-GO1 dosing period and follow-up periods are defined in the table below.

ALN-GO1 Dosing Period and Follow-up Periods

Dosing Regimen	ALN-GO1 Dosing[a]	Postdose Follow-up[b]	Safety and PD Follow-up[c]
Monthly	Day 1 to 85 relative to the first dose of ALN-GO1	Day 85+ to 169 relative to the first dose of ALN-GO1	Day 169+ relative to the first dose of ALN-GO1
Quarterly	Day 1 to 85 relative to the first dose of ALN-GO1 for patients randomized to placebo Day 1 to 169 for patients randomized to ALN-GO1		Day 86+ relative to the first dose of ALN-GO1 for patients randomized to placebo Day 169+ for patients randomized to ALN-GO1

a: Patients receiving ALN-GO1 in single-blind or open-label manner and in any sequence

b: Patients in monthly dosing cohorts

c: Patients in all regimen and dosing cohorts

7.2.3 By-visit Data Presentation

In Part B, the by-visit PD and safety summaries will be presented according to the specifications below.

Monthly Dosing Regimen: Part B

Timepoint[a]	Placebo[b] (N=4)	Monthly ALN-GO1 Single-blind[c] Dose1 (N=3)	Monthly ALN-GO1 Comb.[d] Dose1 (N=4 or 8)	Monthly ALN-GO1 Single-blind[c] Dose2 (N=3)	Monthly ALN-GO1 Comb.[d] Dose2 (N=4 or 8)	Monthly ALN-GO1 Single-blind[c] Total (N=6)	Monthly ALN-GO1 Comb.[d] Total (N=8 or 16)
Baseline[e]							
Day 29							
Day 57							
Day 85[f]							
Day 113	NA						
Day 141	NA						
Day 169[g]	NA						
Day 197[h]	NA						
Day 225	NA						
Day 253	NA						
Day 281	NA						
Day 309	NA						

a: In monthly dosing regimen, patients randomized to ALN-GO1 will be summarized by study day 1 to 85 during the single-blind monthly treatment period, then by post dosing follow-up period after Day 85 and up to Day 169, followed by Safety and PD follow-up after Day 169. Patients randomized to Placebo will be summarized by study day 1 to 85 relative to placebo dosing date during the single-blind treatment period. Data collected after the first dose of ALN-GO1 will be summarized separately by days relative to the first open-label ALN-GO1 dose with all visits for the rest of the study mirrored to the patients randomized to the single-blind ALN-GO1. These data will be summarized in combination with data from patients randomized to ALN-GO1 at each corresponding visit.
b: Patients from all monthly and quarterly dosing cohorts randomized to placebo at study start
c: Patients randomized to ALN-GO1 at study start receiving ALN-GO1 in single-blind manner
d: Patients receiving ALN-GO1 in single-blind or open-label manner and in any sequence combined
e: Baseline is defined as ….. before first dose date/time of each treatment, placebo or ALN-GO1
f: Day 85 is the end of treatment period
g: Day 169 is the end of post-treatment follow-up period
h: Day 197 and later visits are Safety and PD follow-up visits

Quarterly Dosing Regimen: Part B

Timepoint[a]	Placebo[b] (N=4)	Quarterly 2-doses[c] ALN-GO1 Dose1 (N=3)	Quarterly 1-dose[d] ALN-GO1 Dose1 (N=1)	Quarterly Comb.[e] ALN-GO1 Dose1 (N=4)	Quarterly 2-doses[c] ALN-GO1 Dose2 (N=3)	Quarterly 1-dose[d] ALN-GO1 Dose2 (N=1)	Quarterly Comb.[e] ALN-GO1 Dose2 (N=4)	Quarterly 2-doses[c] ALN-GO1 Total (N=6)	Quarterly 1-dose[d] ALN-GO1 Total (N=2)	Quarterly Comb.[e] ALN-GO1 Total (N=8)
Baseline[f]										
Day 29										
Day 57										
Day 85[g]										
Day 113[h]	NA			NA			NA			NA
Day 141	NA			NA			NA			NA
Day 169[i]	NA			NA			NA			NA
Day 197[j]	NA			NA			NA			NA
Day 225	NA			NA			NA			NA
Day 253	NA			NA			NA			NA
Day 281	NA			NA			NA			NA
Day 309	NA			NA			NA			NA

a: In quarterly dosing regimen, patients randomized to ALN-GO1 will be summarized during the treatment period by study days with ALN-GO1 dosing on Day 1 (single-blind) and 85 (open-label) followed by the Safety and PD follow-up period after Day 169. Patient randomized to Placebo will be summarized by days relative to placebo dosing date for the placebo period (Study Days 1-85), and separately by days relative to the open-label ALN-GO1 dosing date for the treatment period (Days 85-169 post placebo dose; Days 1-85 post ALN-GO1 dose), followed by the Safety and PD follow up period after Day 169.
b: Patients from all monthly and quarterly dosing cohorts randomized to placebo at study start
c: Patients randomized to ALN-GO1 at study start. First quarterly GO1 dose is in single-blind manner and the second quarterly GO1 dose is in open-label manner
d: Patients randomized to placebo at study start and received one dose of open-label ALN-GO1 on Day 85, and Days are relative to the open label ALN-GO1 dose.
e: Patients receiving ALN-GO1 in single-blind or open-label manner and in any sequence combined.
f: Baseline is defined as xxxx before first dose date/time of each treatment, placebo or ALN-GO1
g: Day 85 is the end of single-blind treatment period for placebo and 2-doses ALN-GO1 patients, and the end of open-label ALN-GO1 treatment period for 1-dose ALN-GO1 patients
h: Day 113 and later visits are Safety and PD follow-up period for 1-dose ALN-GO1 patients
i: Day 169 is the end of open-label treatment period for 2-doses ALN-GO1 patients
j: Day 197 and later visits are Safety and PD follow-up period for 2-doses ALN-GO1 patients

7.3 Study Population Data

7.3.1 Subject and Patient Disposition

For Part A, the following subject disposition categories will be summarized, if applicable:

- Subjects who were randomized,
- Subjects who were randomized but not treated,
- Subjects who were randomized and treated,
- Subjects who completed/did not complete the single-blind treatment, and
- Subjects who completed/did not complete the study.

Patient disposition will be summarized by initial ALN-GO1 dose level and regimen and in total for all subjects in Part B. Patients in randomized cohorts

For Part B, the following patient disposition categories will be summarized, if applicable:

- Patients who were enrolled,
- Patients who were enrolled but not treated,
- Patients who were enrolled and treated,
- Patients who completed/did not complete the initial/all treatment,
- Patients who completed/did not complete the study.

Patients that signed the informed consent form and met applicable eligibility criteria will be considered as enrolled. For those who did not complete study treatment per protocol and/or did not complete the study, the primary reason for withdrawal will be summarized.

The number and percentage of subjects in each defined analysis population will be tabulated and presented.

All subject disposition data will be presented in a data listing for both Part A and Part B.

7.3.2 Protocol Deviations

All major protocol deviations will be presented in a data listing.

7.3.3 Demographic and Baseline Characteristics

In Part A and Part B, demographic and baseline characteristics will be summarized by regimen (as applicable in Part B) and ascending dose level groups, placebo, and in total for the Safety Analysis Sets. If the PK and PD Analysis Sets contain a different set of subjects/patients compared to those included in the Safety Analysis Set, then demographic information will be summarized separately for those analysis sets.

The following variables will be considered based on their collection at screening. Gender, race, and ethnicity will be summarized with contingency tables. Age at screening (years), height, weight, and body mass index (BMI) at baseline will be presented with appropriate summary statistics (n, mean, median, SD, minimum, maximum). See Section 6.1.3 for height and weight baseline definition. Patients <18 years of age at screening Part B will have the modified z-score calculated for their height, weight, and BMI according to the Centers for Disease Control growth chart [1] and will be presented with summary statistics.

For Part B patients, the 24-hour urinary oxalate excretion (mmol/24 hours/1.73m^2) and eGFR at baseline will be summarized descriptively by dose level groups, placebo, and in total. Separate analyses will be provided for patients less than 18 years of age and patients 18 years or older at informed consent.

The number and percentage of subject who took vitamin B6 within 90 days of informed consent and/or during the study will be tabulated.

Summary tables will be presented by ascending ALN-GO1 dose level with subjects/patients receiving placebo pooled across enrollment cohort and in total.

By-subject data listings of demographic information will be presented for Part A and Part B.

7.3.4 Medical History

A complete medical and surgical history will be collected at the screening visit. The medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 19.1 or Higher).

Medical and surgical history will be summarized for the Safety Analysis Sets for Part A and Part B by system organ class and preferred term for each dose level groups and placebo and overall.

For Part A and Part B, all medical/surgical history will be presented in by-subject listings for all randomized subjects.

7.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (October 2016 or later). Prior medications are defined as medications that were taken prior to and stopped before the first dose of the study medication. Concomitant medications are defined as medications that were taken on or after the first dose date of the study medication.

The number and percentage of subjects taking concomitant medications will be summarized by anatomic therapeutic class (ATC) and preferred term. Data will be presented by dose level and placebo for the Safety Analysis Sets in Part A and Part B. In addition, for Part B, concomitant medications will also be summarized in the same manner by dose level of ALN-GO1 using combined data from both the blinded portion and the open-label portion.

For Part A and Part B, prior and concomitant medications will be presented in by-subject listings.

7.4 Safety Analysis

The primary objective of the study is to assess the safety and tolerability of ALN-GO1 in healthy adult subjects and patients with a confirmed diagnosis of PH1. Safety analyses will include the summarization of Adverse Events (including Serious Adverse Events and Treatment-Emergent Adverse Events), exposure to study drug, vital signs, physical examination findings, ECG parameters, echocardiograms (Part B only), clinical laboratory assessments, and other safety variables. All safety analyses will be based on the Safety Analysis Sets.

7.4.1 Adverse Events

In Part A, summary tables for AEs will be presented by ascending ALN-GO1 dose level, in total with all subjects receiving ALN-GO1, and placebo with subjects/patients receiving placebo pooled across enrollment cohorts presented first. AEs will be summarized separately for the single-blind dosing period and the study.

In Part B, for patients who were randomized to placebo, an AE during the single-blind period is defined as an AE with onset date/time on and after the first dose date/time of placebo and prior to the first dose date/time of open-label ALN-GO1. For patients who were initially randomized to ALN-GO1 a AE during the single-blind period is defined as an AE with onset date/time on or after the first dose date/time of ALN-GO1 and up to, and including, Study Day 85. AEs for single-blind period will be summarized by regimen and ascending dose level of ALN-GO1 and pooled placebo across regimen and dose being presented first. Sub-total for each regimen and overall will also be presented.

In Part B, a summary of AEs for the single-blind period will be provided by regimen and ascending dose level of ALN-GO1 and pooled placebo presented first. Total for each regimen and overall of ALN-GO1 will also be provided.

In Part B, for all patients receiving ALN-GO1, either as single-blind or open-label administration, and in any sequence, a AE is defined as an AE with onset date/time on or after the first dose date/time of ALN-GO1 and up to the end of study. All AEs under ALN-GO1 will be summarized by regimen and ascending dose, sub-total for each regimen, and for overall. At each dose level and for the sub-total and overall, AEs with be summarized for patients with single-blind administration only and then for single-blind and open-label administration combined.

In each analysis above, an overview of adverse events will be provided which summarizes subject-level incidence (frequency) of all AEs, drug-related AEs, grade 3/4/5 AEs, drug-related grade 3/4/5 AEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, and AEs leading to discontinuation of study drug and/or deaths.

The number and percentage of subjects with AEs will be summarized by system organ class and preferred term. Drug-related AEs, grade 3/4/5 AEs, drug-related grade 3/4/5 AEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, AEs leading to discontinuation of study drug, AEs leading to study drug dose interruption and drug-related AEs leading to discontinuation of study drug will be summarized by system organ class and preferred term. For these summaries, subjects with multiple adverse events will be counted only once per SOC and preferred term. Summaries of AEs leading to discontinuation of study drug and leading to study drug dose interruption will be presented as applicable for the single-blind period, ALN-GO1 dosing period, and ALN-GO1 quarterly dosing period. Other summaries will be presented separately for the time periods in Sections 7.2.1 and 7.2.2.

In addition, summaries will be provided by the worst NCI-CTCAE grade, system organ class and preferred term for the number and percentage of subjects with AEs and drug-related AEs.

Listings will be provided for AEs leading to deaths, SAEs, and AEs leading to discontinuation of study drug or dose interruption.

By-subject AE data listings which will include at a minimum, subject/patient identifier, study drug taken prior to or on an AE onset date/time, verbatim term, preferred term, system organ class, NCI-CTCAE grade, relationship to study drug, action taken with study drug, SAE classification (Yes/No) and AE onset and end date/time. In addition, for Part A, AE and study day will also be included. In Part B, classification (yes/no) as a AE during the single-blind dosing period and the ALN-GO1 dosing period will be included. In Part B, study day and day relative to ALN-GO1 dosing will be included.

By-subject AE listings will be provided for Part A and Part B separately.

7.4.2 Dosing and Extent of Exposure

The actual dose administered and the number of injections will be summarized descriptively by dose level (or placebo) and overall for the Safety Analysis Set in Part A. Compliance with study drug administration is not relevant as all doses will be administered by qualified clinical study site personnel and recorded on the electronic Case Report Form.

Part B consists of three doses of study drug on Days 1, 29, and 57 for monthly dosing cohorts. For patients who randomized to placebo and crossed over to ALN-GO1 during the open label portion, study drug will be administered on Days 85, 113, and 141. Patients who randomized to receive ALN-GO1 will receive study treatment in a single-blind manner while patients enrolled in expansion cohorts will receive ALN-GO1 in an open-label manner.

In Part B for quarterly dosing cohorts, patients will receive either ALN-GO1 or placebo according to the randomized treatment assignment on Day 1. All patients in quarterly dosing cohorts, including those randomized to placebo, will receive open-label ALN-GO1 on Day 85 at the same dose administered to the cohort into which they were initially randomized.

Treatment duration of study drug in Part B is defined as:

- For patients randomized to placebo in monthly or quarterly cohorts, treatment duration of placebo is min (first dose date of open-label ALN-GO1 or visit date of Day 85 visit) – first dose date of placebo +1
- For patients in monthly dosing regimen, treatment duration of ALN-GO1 is the visit date of Day 85 relative to first dose of ALN-GO1 – first dose date of ALN-GO1 +1
- For patients randomized to placebo in quarterly dosing cohorts, their treatment duration of open-label ALN-GO1 is the same as for monthly dosing regimen.

- For patients randomized to ALN-GO1 in quarterly dosing cohorts, the single-blind treatment duration is Day 85 visit date – first dosed date of ALN-GO1 +1 and the total ALN-GO1 treatment duration is Day 169 visit date – first dose date of ALN-GO1 +1.

Treatment duration of study drug will be summarized using descriptive statistics by regimen, ascending dose level of ALN-GO1, pooled placebo, and in total for the single-blind time period and total ALN-GO1 dosing period.

In Part B, dosing status will be tabulated by regimen and dose level (including placebo during the summary for the single-blind study period). The following categories will be summarized:

- Subjects with a missed dose,
- Subjects with a dose interruption

The above summary will be provided in Part B for the single-blind dosing period by pooled placebo, regimen, and ascending ALN-GO1 dose. The above summary will be provided separately for the ALN-GO1 dosing period (by regimen and ascending ALN-GO1 dose, regardless of treatment sequence) and ALN-GO1 quarterly open-label dosing period.

In Part A and Part B, all study drug administration information will be listed.

7.4.3 Clinical Laboratory Assessments

Where applicable, abnormal laboratory results will be graded according to NCI CTCAE v4.0. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value according to the NCI CTCAE grade, will be provided for selected clinical laboratory tests. Both scheduled and unscheduled post-baseline values will be considered.

For Part A, descriptive statistics will be provided for clinical laboratory data for actual results, changes from baseline, and relative to the upper limit of normal range (ULN) over time by pooled placebo and ascending ALN-GO1 dose.

For Part B, descriptive statistics will be provided for clinical laboratory data for actual results, changes from baseline and relative to the upper limit of normal range over time according to the data display specification in Section 7.2.

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

This categorical data will also be summarized in shift tables comparing the worst value post-baseline with those at the baseline visit. When there are both high and low abnormal values for a subject for a particular laboratory variable, the worst value will be taken (the value furthest outside of the normal ranges, or the first value experienced, if this value is the same). In Part A, frequencies and percentages will be presented by dose group. In Part B, shift table will be

summarized by pooled placebo and ascending single-blind ALN-GO1 dose and by ALN-GO1 dose in single-blind and open-label combined.

All clinical laboratory data in Part A and Part B will be listed.

7.4.4 Vital Signs

For Part A and B, systolic blood pressure, diastolic blood pressure, pulse rate, body temperature, respiratory rate, height (Part B only), and body weight will be summarized as actual values and changes from baseline in the same way as described in Sections 7.1 (Part A) and Section 7.2.1-2 (Part B). Patients<18 years of age in Part B at enrollment will have the modified z-score calculated for their height, weight, and BMI according to CDC growth chart [1].

Separate summaries will be provided in Part B for the single-blind dosing period (by pooled placebo, regimen, and ascending ALN-GO1 dose), the ALN-GO1 dosing period (by regimen and ascending ALN-GO1 dose, regardless of treatment sequence), and the post-dose, safety, and PD follow-up period (by regimen and ascending ALN-GO1 dose, regardless of treatment sequence) as described in Sections 7.2.1-7.2.2.

All vital signs data in Part A and Part B will be listed.

7.4.5 Physical Examinations

For both Part A and Part B, physical examination findings, including any abnormal findings, will be listed. All data from symptom-directed physical examinations will be listed.

For Part B, all data from symptom-related physical examinations will be listed.

7.4.6 ECGs

Analyses of ECGs for both Part A and Part B and will be based on the Safety Analysis Sets.

In Part A, analyses will be presented separately for the single-blind dosing period and safety and PD follow-up period. In Part B, analyses will be presented separately for the single-blind dosing period (by pooled placebo, regimen, and ascending ALN-GO1 dose), ALN-GO1 dosing period (by regimen and ascending ALN-GO1 dose, regardless of treatment sequence), quarterly open-label ALN-GO1 dosing period (by ascending ALN-GO1 dose), postdose follow-up period (by ascending ALN-GO1 dose), and Safety and PD follow-up period (by regimen and ascending ALN-GO1 dose, regardless of treatment sequence).

Subjects with the following diagnoses or abnormal ECG findings will be excluded from the ECG analysis: artificial pacemaker (recorded as presence of atrial pacing, ventricular pacing, and/or atrial ventricular pacing), atrial fibrillation (or flutter), left bundle branch block (complete or incomplete), and right bundle branch block (complete or incomplete).

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

For both Part A and Part B, electrocardiogram parameters (ventricular rate, PR, QRS, QT, QT_cB, and QT_cF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation (given in the Schedule of Assessments). These summaries will be presented separately for the time periods in Sections 7.1 (Part A) and Sections 7.2.1-2 (Part B).

Baseline, post baseline maximum QTcF, and post baseline maximum change from baseline in QTcF during the study will be summarized with descriptive statistics. The incidence of notable ECG changes from baseline in maximum absolute QT, QT_cF, and QT_cB intervals (<=450, > 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QT, QT_cF, and QT_cB maximum changes from baseline (> 30 and > 60 ms) over all post-treatment evaluations will be summarized by dose level of ALN-GO1, pooled placebo, and overall for all subjects receiving ALN-GO1 in Part A. In Part B, the summary will be presented by regimen and ascending ALN-GO1 dose level, regardless of treatment sequence.

Scatterplots of QT Interval by RR Interval, QTcF Interval by RR Interval, and QTcB Interval by RR Interval will be presented for the pooled placebo and by regimen and by dose groups. For each QTcF Interval that has a time-matched pharmacokinetic concentration, a scatterplot of change from baseline QTcF Interval by concentration will be presented for the pooled placebo and by regimen and by dose groups. The line produced from simple linear regression will be used as a line of reverence.

A listing of all ECG data will be provided.

7.4.7 Echocardiograms (Part B Only)

Summary statistics (n, mean, median, SD, minimum, maximum) will be presented for the baseline measurement of Left Ventricular Ejection Fraction.

The number of patients with clinically significant changes in systolic function will be tabulated for each on-study assessment separately by ascending ALN-GO1 dose level and regimen and placebo for the single-blind dosing period.

All ECHO assessments will be listed by subject in the order of ascending ALN-GO1 dose and placebo.

7.4.8 Analysis of Other Safety Variables

For both Part A and Part B, all other safety data will be listed.

7.5 Pharmacokinetic Analyses

PK analyses will be performed based on the PK Analysis Set. All PK summaries will be presented by dose level of ALN-GO1. For Part B, the PK data of ALN-GO1 from both the blinded and open-label portion will be combined at each dose level.

Plasma and urine PK concentration data of ALN-GO1 will be summarized at each scheduled time point by dose level using descriptive statistics (n, mean, standard deviation [SD], standard error [SE], minimum, maximum, median, and percent coefficient of variation [%CV]). Mean plasma concentrations of ALN-GO1 versus nominal time will be plotted by dose level and study day on both linear scale and semi-logarithm scale. Individual plasma concentration versus actual time plots will also be provided. Individual and mean plasma concentrations of ALN-GO1 versus nominal time will also be plotted by dose level, study day and ADA status on both linear scale and semi-logarithm scale.

The plasma PK parameters and urine PK parameters of ALN-GO1 following single dose on Day 1 in Part A, single dose on Day 1 relative to ALN-GO1 dosing (Part B monthly and quarterly cohorts), multiple doses on Day 57 relative to ALN-GO1 dosing (Part B monthly cohorts only), and multiple doses on Day 85 relative to ALN-GO1 dosing (Part B quarterly cohorts only) will be summarized by regimen and ascending dose level. Geometric mean and geometric coefficient of variation will be added to the descriptive statistics for calculated PK parameters.

All individual subject plasma and urine concentrations data and actual sampling times will be listed. All PK parameters will be listed by subject, dose level, study day and ADA status.

7.6 Pharmacodynamic and Exploratory Analyses

Pharmacodynamic parameters will be measured from blood and urine samples collected at times outlined in the Schedule of Assessments in both Part A and Part B. PD analyses will be based on the Pharmacodynamic Analysis Sets.

24-hour urine oxalate content corrected for BSA will be calculated as:

> [24-hour urine oxalate in mmol/L]*[24-hour urine volume recorded in CRF in ml]
> /(1000 ml per L)*24hours/[actual collection time calculated from CRF in hours]
> *1.73/[patient BSA]
>
> Where patient BSA will be calculated as:
>
> Patient BSA = sqrt([mean height in cm] *[weight in kg] /3600).

24-hour urine creatinine clearance corrected for BSA will be calculated as:

> [24-hour urine creatinine concentration in mg/dl]*[24-hour urine volume recorded in CRF in ml]
> /[Plasma creatinine in mg/dl]/[actual collection time calculated from CRF in minutes]
> *1.73/[patient BSA]24-hour urine oxalate/creatinine ratio will be calculated as:
> 24-hour urine oxalate concentration (mg/L) /24-hour urine creatinine concentration (mg/dL)/10.

For Part A and Part B, the mean and standard error of actual values and changes from baseline in plasma and urine glycolate will be plotted over time by ALN-GO1 dose level and placebo. In

addition, plots will be provided for plasma and urine glycolate of individual subjects by dose level of ALN-GO1 and placebo.

For Part B, the mean and standard error of actual values and changes from baseline in urinary oxalate per 24-hour urine collection and urinary creatinine per 24-hour urine collection will be plotted over time. In addition, the plots will be presented separately by ADA status. Plasma glycolate concentration and oxalate/creatinine ratio will be plotted in the same manner. For patients randomized to placebo, figures will include PD measurements up to the first dose of open-label study drug.

For other PD variables in Part A and B, descriptive statistics will be provided for actual results, change from baseline, and percent change from baseline. For Part B, the PD summaries will be presented according to the data display specification in Section 7.2.3.For Part A and Part B, Cmax and AUCt of plasma glycolate will be presented with descriptive statistics and percent coefficient of variation [%CV]) by regimen and ascending dose level and placebo presented first.

In Part A and Part B, all PD data will be listed by regimen, dose, ADA status (Part B only) and subject/patient.

7.7 Immunogenicity Analysis

For Part A and Part B, results from tests for antidrug antibodies will be listed by subject in the order of ascending ALN-GO1 dose and placebo for the Safety Analysis Sets.

8 GENERAL INFORMATION

8.1 Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.3 or higher. The Medpace standard operating procedures (Medpace documents [redacted]) will be followed for the validation of all SAS programs and outputs. Pharmacokinetic parameters will be derived at Alnylam Pharmaceuticals using Phoenix WinNonlin software Version 7.0 or higher.

8.2 Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document and will be finalized before database lock for the study.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

No changes have been issued or planned.

10 REFERENCES

References are provided in the study Protocol.

[1] CDC Growth Chart https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm