Cover Page for SAP

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Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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Statistical Analysis Plan

A Phase 2 Open-Label Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Nedosiran in Pediatric Patients from Birth to 11 Years of Age with Primary Hyperoxaluria and Relatively Intact Renal Function

Substance: Nedosiran / DCR-PHXC

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Protocol Title:	A Phase 2 Open-Label Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Nedosiran in Pediatric Patients from Birth to 11 Years of Age with Primary Hyperoxaluria and Relatively Intact Renal Function
Sponsor:	Novo Nordisk, Inc. 75 Hayden Avenue Lexington, MA 02421 US
Protocol Number:	DCR-PHXC-203
Date/Version:	23-Feb-2023 V4.0
Author:	[redacted] _____ 22-Jan-2024 _____ Signature Date Name: [redacted] Title: [redacted] Biostatistics Company: Novo Nordisk, Inc.

Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

Approved by:	[redacted] _____ 22-Jan-2024 _____ Signature Date Name: [redacted] Title: [redacted], Biostatistics Company: Novo Nordisk, Inc.
	[redacted] _____ 22-Jan-2024 _____ Signature Date Name: [redacted] Title: [redacted] Company: Novo Nordisk, Inc.

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Version History

This Statistical Analysis Plan (SAP) for study NN7022-PHYOX8 (Dicerna protocol number DCR-PHXC-203) is based on the protocol version V4.0, dated 23-Feb-2023.

SAP Version	Date	Change	Rationale
V2.0	12-Jan-2024	Update age groups for analysis from (0-5, 6-11) to (0 - <2, 2-< 6, 6-<9, 9-11)	Update age groups for analysis following FDA sNDA feedback.
V2.0	12-Jan-2024	Replace the categorical age groups with continuous age as covariate for MMRM modelling in Section 4.2.2	Considering that there are limited number of patients within each updated age group, continuous age variable may be used as a covariate in MMRM modelling.
V2.0	12-Jan-2024	Add sensitivity analysis on the ratio of spot urinary oxalate-to-creatinine ratio to the ULN in Section 4.2.3	Perform additional sensitivity analysis to adjust for the any potential confounding effect of natural maturity on spot urinary oxalate-to-creatinine ratio following FDA sNDA feedback.
V2.0	12-Jan-2024	Update MITT definition to include all PH types	Efficacy will be summarized by PH type.
V2.0	12-Jan-2024	The safety analysis of interim analysis will be based on Safety Analysis Set	All safety data will be included in the interim analysis following FDA sNDA feedback.

List of abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events special interest
ATC	anatomical therapeutic chemical
AUC	area under the curve
BLQ	below the limit of quantitation
BSA	body surface area
CRF	case report form
CS	clinically significant
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
HR	heart rate
HRQOL	health related quality of life
IC or ICF	informed consent or informed consent form
ICH	International Council for Harmonization
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
N	number
PD	pharmacodynamic

Abbreviation	Definition
PE	physical examination
PH	primary hyperoxaluria
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PT	preferred term
QOL	quality of life
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization drug dictionary

1 Introduction

This statistical analysis plan (SAP) describes the planned analysis and reporting for Dicerna protocol number DCR-PHXC-203 (A Phase 2 Open-Label Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Nedosiran in Pediatric Patients from Birth to 11 Years of Age with Primary Hyperoxaluria and Relatively Intact Renal Function), protocol amendment V4.0, dated 23-Feb-2023.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified in the final CSR.

This SAP is an *a priori* plan. It will be finalized and signed off prior to clinical database lock of study DCR-PHXC-203.

Specifications of tables, figures, and listings (TFL) and other specifications not included in this SAP will be described in the mock TFL.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of nedosiran in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Percent and absolute change from Baseline to Month 6 in spot urinary oxalate-to-creatinine ratio in PH1, PH2, or PH3 participant subgroups
Secondary	
• To characterize the safety of nedosiran in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• The incidence and nature of TEAEs and SAEs • Change from Baseline in 12-lead ECG, physical examination findings, vital sign assessments, and clinical laboratory tests
• To characterize the PK of nedosiran in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Plasma PK parameters for nedosiran and/or its metabolites, including C_{max}, AUC_t and AUC_∞ (if estimable)
• To assess the efficacy of nedosiran in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Percentage of participants with spot urinary oxalate-to-creatinine ratio ≤ the ULN or ≤ 1.5 x ULN at any time point through Month 6 in PH1, PH2, or PH3 participant subgroups
• To evaluate the effect of nedosiran on eGFR in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Change from Baseline in eGFR at Month 6 (only in participants ≥ 12 Months of age at Screening) in PH1, PH2, or PH3 participant subgroups
Tertiary/Exploratory	
• To assess the effect of nedosiran on plasma oxalate in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Percent and absolute change in plasma oxalate over time in PH1, PH2, or PH3 participant subgroups
• To assess the effect of nedosiran on stone events in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Change from Baseline in annualized stone event rate in PH1, PH2, or PH3 participant subgroups
• To evaluate the effect of nedosiran on QoL assessments in neonates, infants, and children with PH and relatively intact renal function based upon eGFR and serum creatinine	• Change from Baseline in the Pediatric Quality of Life Inventory (PedsQL™) in PH1, PH2, or PH3 participant subgroups
• To evaluate the effect of nedosiran on productivity loss of caregivers for neonates, infants, and children with PH and relatively	• Change from Baseline in the Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0,

Objectives	Endpoints
intact renal function based upon eGFR and serum creatinine	Clinical Practice Version (WPAI:PH, V2.0, CPV) – Caregiver in PH1, PH2, or PH3 participant subgroups

1.1.2 Primary Estimand

The primary clinical question of interest is: What is the treatment effect of nedosiran in lowering urinary oxalate excretion (Uox) assessed via percent change from baseline in spot urinary oxalate-to-creatinine ratio at Month 6 in PH1 pediatric participants (birth to 11 years of age) with relatively intact renal function.

For the primary objective, the estimand is defined with five attributes:

- Treatment condition of interest is the monthly nedosiran administration.
- The target population is PH1 pediatric participants (birth to 11 years of age) with relatively intact renal function.
- The endpoint is percent change from baseline at Month 6 in spot urinary oxalate-to-creatinine ratio.
- The intercurrent events (ICEs) include treatment discontinuation for any reasons and will be handled by the treatment policy strategy.

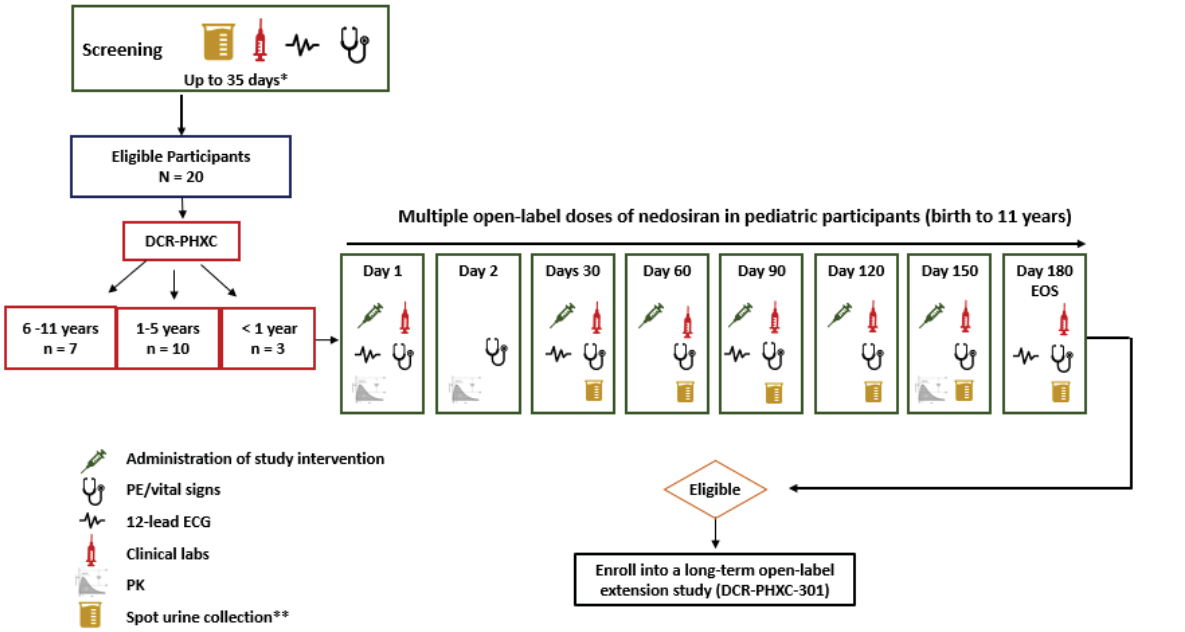
Population-level summary is the percent change from baseline at Month 6 estimated by Mixed-effect Model Repeated Measures (MMRM) approach.

Rationale for estimand: The primary estimand assesses the treatment benefit of nedosiran in lowering urinary oxalate-to-creatinine ratio that can be expected in clinical practice, provided that the treatment adherence in the study reflects what would be seen in clinical practice.

1.2 Study Design

This is a Phase 2, multi-dose (3.5 mg/kg, not to exceed 170 mg), open-label, single-arm uncontrolled multi-center study of nedosiran in pediatric participants (birth to 11 years of age) with genetically confirmed PH1, PH2, or PH3, with relatively intact renal function based upon eGFR and serum creatinine.

Figure 1: Schematic design of trial



* An additional 7 days of screening may be added for participants who require repeated initially unanalyzable screening laboratory assessment samples
**Spot urine collection will include 6 samples at Screening and 4 samples at all other time points indicated in the schema

2 Statistical Hypotheses

No confirmatory testing will be done in this study.

2.1 Multiplicity Adjustment

Not applicable.

3 Analysis Sets

The following analysis populations are planned for this study:

Participant Analysis Set	Description
Safety Population (SAF)	• The safety population includes all participants who received at least 1 dose of study intervention.
Modified Intent-To-Treat Population (MITT)	• The MITT population includes all participants who received at least 1 dose of study intervention and have at least 1 post-baseline spot urinary oxalate to creatinine ratio. The MITT population is for efficacy analysis.
Evaluable Population (EVAL)	• The evaluable population includes all participants in the MITT population who received 6 full doses of study intervention and completed through the Day 180 Study Visit.
Pharmacokinetic Population (PK)	• The PK population will be defined in PK analysis plan (PKAP).
Per-Protocol Population (PP)	• The PP population includes all PH1 participants who received at least 1 dose of study intervention and had no major protocol deviations that affect efficacy endpoint assessment as adjudicated by the sponsor.
Interim Analysis Population	• The Interim Analysis population includes first 15 PH1 participants who completed the study.

4 Statistical Analyses

4.1 General Considerations

4.1.1 General Considerations for Analyses

4.1.1.1 Study Day

Study Day 1 is defined as the first dose date (i.e., date of first administration of study intervention). The first dose date is used as the reference start date for analysis.

For days prior to Study Day 1, Study Day = reference date – first dose date.

For days on or following Study Day 1, Study Day = reference date – first dose date + 1.

4.1.1.2 Baseline

For all endpoints (except spot urinary oxalate-to-creatinine ratio and annualized stone events rate), the last non-missing observation recorded prior to the first dose of study intervention will be used as the baseline observation for all calculations of change from baseline.

For assessments where the time is not collected (like QoL questionnaires), the last observation recorded prior or during the day of the first dose will be considered as baseline.

For spot urinary oxalate-to-creatinine ratio (including spot urinary oxalate and creatinine measurements), the average of all available spot urine samples (retest samples will be used if available) collected at screening will be used as baseline value.

For annualized stone events rate, baseline will be the number of stone events observed over the past 12 months prior to screening.

Any measure assessed after the date/time of the first dose will be considered as post baseline assessments.

4.1.1.3 Handling of Dropouts or Missing Data

4.1.1.3.1 Missing Efficacy Endpoint Data

While all possible efforts will be made to ensure that participants stay in the study and all data is collected as scheduled, the occurrence of missing data cannot be eliminated.

Participants who sign the informed consent form but do not receive the study intervention may be replaced. Should there be a participant(s) who signs the informed consent form, and receives the study intervention and subsequently withdraws, or is withdrawn or discontinued from the study before the Day 180 Visit, an additional participant(s) in the same age group may be enrolled to ensure that an adequate number of participants complete the Day 180 visit assessments.

No other imputation will be used in the study except for partial dates described in Section 4.1.1.7.

4.1.1.4 Handling of Rescreened Participants

Rescreening of participants is allowed with approval of the Sponsor. If a patient initially screen fails and is subsequently enrolled then that participant will have two subject IDs within the EDC system (one ID XXX-XXXA for the screen failure and associated data collection, and one ID XXX-XXXB for the subsequently enrolled participant).

4.1.1.5 Analysis Visit Windows

By-visit summaries will be based on electronic case report form (eCRF)-defined nominal visits.

In general, analysis of all variables for this study will use the nominal visit or time point as collected on the electronic case report form (eCRF) and/or database. Scheduled visits will be selected over unscheduled visits.

For those participants who discontinue early from the study and the Early Termination (ET) visit satisfies the following condition:

- 20 days <= the date of ET - the date of the last visit before ET +1 <= 40 days

then the ET visit will be mapped to the next scheduled visit. Otherwise, the ET will not be mapped into any analysis visits.

4.1.1.6 Derived Variables

- Change from baseline = value at current time point – baseline value
- Percentage change from baseline = $\left(\frac{value\ at\ current\ time\ point - baseline\ value}{baseline\ value}\right) * 100\%$
- Spot urinary oxalate-to-creatinine ratio = the average of all the spot urinary oxalate-to-creatinine ratio collected at the specific visit.
- Treatment-emergent AE (TEAE) = any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and until the study completion date from the end of study CRF.
- Body surface area will be calculated using the following formula (DuBois & DuBois, 1916):

  BSA = $(Weight^{0.425} \times Height^{0.725}) \times 0.007184$; with weight in kilograms and height in centimeters.
- Body mass index (BMI) will be calculated using the formula: Weight [kg]/(Height^2 [m^2]).
- Estimated Glomerular Filtration Rate (eGFR) will be calculated as described in Protocol Section 8.2.6.1.
- Annualized stone event rate will be derived as number of stone events in the exposure period / total number of years exposed.

  The number of stone events will be calculated as the number of discreet (non-concurrent) adverse events marked as a Kidney Stone Event on the adverse event CRF. Kidney stone events include renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring medication.

Concurrent events will be defined as events occurring within the same 4-week (28-day) window. For example, renal colic treated with medication on Monday 12 November 2019 followed by stone passage without hematuria on Friday 30 November 2019 is a single (concurrent) stone event (18 days between start and stop of single stone event). Renal colic treated with medication on Monday 12 November 2019 followed by stone passage without hematuria on Wednesday 13 December 2019 is considered two separate stone events (30 days between discreet event one and event two).

- Quality-of-life Questionnaires:

PedsQL

The PedsQL™ is a modular approach to measuring health related quality of life (HRQOL) in healthy children and adolescents and in those with acute and chronic health conditions. The multidimensional PedsQL Generic Core Scales were designed to measure the 3 core dimensions of health as delineated by the World Health Organization (WHO) in 1948 (physical, emotional, and social functioning), as well as role (school) functioning[4,5,6].

Questionnaires are administered to the participant and the participant's parent. The 23-item PedsQL™ is comprised of 5 items in the Emotional, Social and School Functioning dimensions (Psychosocial Health) and 8 items in the Physical Functioning (Physical Health) dimension. The questionnaire has specific versions for the child and the child's parent based on the age of the participant (5-7 years old, 8-12 years old, 13-18 years old). Questionnaires are administered based on the age of participant at baseline. The same version of the questionnaire will be used throughout the course of the study for a given participant based on age at baseline. Additionally, the family impact module is administered to the participant's parent.

Items are reverse-scored on a 0 to 4 Likert scale and linearly transformed to a 0 to 100 scale. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. Higher scores indicate better functioning and HRQOL. Further details and scoring instructions are provided in a separate document.

WPAI:PH, V2.0, CPV – Caregiver

Refer to details in Protocol Section 8.10.1.

4.1.1.7 Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

Missing or Partial Dates/Times for Adverse Events (AE) and Prior/Concomitant Medications (CM)

The following list describes how partially missing date information will be handled as it relates to partial or missing AE start dates. Similar rules are applied to handle the missing

dates of prior/concomitant medications. The Partial AE start dates will be imputed as the following:

1. If year is not missing and is after the year of first dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first dose:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.
    c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.
3. If year is missing, then impute the year as the year of the first dose date:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, then impute the day as the day of the first dose date.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first dose date then impute the start date as the first dose date.
5. For any cases involving the rules above, if the AE end date is before the AE start date and AE end date is on or after the first dose date, then leave the AE start date missing and assume that AE is treatment emergent for the purpose of the analysis. Further, if the AE stop date is complete and occurs prior to first dose date, leave the AE start date missing and assume that AE is <u>not</u> treatment emergent.

Dates will not be imputed if not considered potentially treatment-emergent. For example, if the AE year matches that of the first dose date but the AE month is prior to that of the first dose date the event is not considered potentially treatment-emergent and no imputed date will be assigned. No imputations will be applied to AE stop dates. No imputations will be applied to AE start or stop times.

Imputation for medication start dates will be handled similarly.

Relationship of the AE to study intervention and intensity will not be imputed for analyses.

Imputation rules in handling the partial or missing Prior/CM end dates are listed below:

1. If the Prior/CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, the imputed Prior/ CM end date will be set to NULL.
2. If the Prior/ CM end date year is not missing and is the same or after the year of first dose date:
    a. If the Prior/ CM end date month is missing, the imputed end date should be set to the earliest of the ‘last treatment follow-up date’, ‘31DecYYYY’, and ‘date of death’.
    b. If the Prior/ CM end date day is missing, the imputed end date should be set to the earliest of the ‘last treatment follow-up date’, ‘last day of the month’, and ‘date of death’.

3. If the imputed Prior/ CM end date is less than the existing Prior/ CM start date, use the Prior/ CM start date as the imputed Prior/ CM end date. Further, if the Prior/ CM end date is complete and occurs after the first dose date, leave the Prior/ CM start date missing and assume that medication is a concomitant medication.

4.1.2 Disposition of Participants and Withdrawals

Disposition will include tabulations for the number of participants screened and screen failed; the number and percentage of participants who: received treatment, completed study, reasons for study discontinuation/withdrawal (overall and by reason for study discontinuation/withdrawal); the number and percentage of participants in each analysis population will also be displayed. All the tabulations will be for SAF and by PH type and age group (0-<2, 2 - < 6, 6-<9, and 9 - 11 years).

4.1.3 Protocol Violations and Deviations

Prior to database lock, all protocol deviations will be reviewed, categorized as either 'Important' or 'Non-important', and finalized. Protocol deviations will be listed and summarized descriptively. All the tabulations will be for SAF and by PH type and age group (0-<2, 2 - < 6, 6-<9, and 9 - 11 years).

4.1.4 Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity (where available, as ethnicity may not be collected at all sites), height/length, weight, and BSA will be presented for SAF and by PH type and age group (0-<2, 2 - < 6, 6-<9, and 9 - 11 years). Body mass index and body surface area will be computed as described in Section 4.1.1.6.

Summary statistics will be presented for baseline eGFR, time since PH diagnosis, number of kidney stone events in the last 12 months, and the number of kidney stones at baseline.

These summaries will be conducted for the MITT and SAF populations. All collected demographics and other baseline characteristics will be listed by participant.

The number and percentage of participants reporting various medical histories, grouped by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (MedDRA; Version 26.0 or higher), will be tabulated for SAF and by PH type and age group.

Prior medications will be presented separately from concomitant medications. Medications that started prior to dosing on Day 1 will be considered prior medications whether they were stopped prior to Day 1 dosing or not. Missing dates will be handled using the methodology described in Section 4.1.1.7. Medications will be coded using World Health Organization drug dictionary (WHO-DD) version March 2023 or later. The number and percentage of participants reporting prior medication and concomitant medication use, grouped by ATC Level 2 and ATC Level 4, will be tabulated by PH type and age group. This analysis will be conducted for the SAF population. The prior medications and concomitant medications will be provided in a listing.

4.2 Primary Estimand Analyses

4.2.1 Definition of Endpoint

The primary endpoint is the percent change from baseline at Month 6 in spot urinary oxalate-to-creatinine ratio. The percent change from baseline at Month 6 in spot urinary oxalate-to-creatinine ratio will be calculated using formulas in section 4.1.1.6.

4.2.2 Main Analytical Approach

The primary analysis of the primary endpoint will be performed for MITT using a restricted maximum likelihood (REML) based MMRM approach with percent change from baseline at scheduled visits (Month 1 – Month 6) as the dependent variable. Analysis will include fixed effects of scheduled visits, baseline spot urinary oxalate-to-creatinine ratio, baseline age and baseline eGFR. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation. A compound symmetry (CS) covariance structure will be used to model the within-patient error given the small sample size for this study. The primary estimate is the least square (LS) mean of the percent change from baseline at Month 6. This LS mean will be presented along with corresponding standard errors (SEMs) and 95% confidence intervals (CI). Similar analysis will be performed to estimate the LS mean of the percent change from baseline averaged over Month 3 to Month 6.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) for MITT population by PH type and by age group (0-<2, 2 - < 6, 6-<9, and 9 - 11 years) will also be provided.

4.2.3 Sensitivity Analyses

As sensitivity analyses, the same analyses as described in Section 4.2.2 will be performed for the EVAL population and PP population. Also, the same analyses as described in Section 4.2.2 will be performed by imputing creatinine measurements or urine oxalate values reported as '<x' where x is the lower limit of quantification (LLOQ) value.

Similar analyses will be performed for absolute change from baseline at Month 6 and averaged over Month 3 to Month 6 in spot urinary oxalate-to-creatinine ratio for MITT population, EVAL population, and PP population.

To further adjust for the any potential confounding effect of natural maturity on spot urinary oxalate-to-creatinine ratio, similar analyses will be performed on the ratio of spot urinary oxalate-to-creatinine ratio to the ULN tailored to individual patient's age for MITT population, EVAL population, and PP population.

4.3 Secondary Endpoints Analyses

4.3.1 Supportive Secondary Endpoints

4.3.1.1 Secondary Endpoints in Efficacy

The secondary endpoints in efficacy listed below will be summarized for MITT by PH type and by age group.

- The percentage of participants with spot urinary oxalate-to-creatinine ratio ≤ the ULN or ≤ 1.5 x ULN at any time point through Month 6 will be summarized (n, %).

- The percent change from baseline in eGFR at Month 6 (only in participants ≥ 12 Months of age at Screening) will be summarized (n, mean, standard deviation, median, minimum, maximum).

4.3.1.2 Secondary Endpoints in Safety

The secondary endpoints in safety are listed below:

- The incidence and nature of TEAEs and SAEs.
- Change from Baseline in 12-lead ECG, physical examination findings, vital sign assessments, and clinical laboratory tests.

All safety analyses will be performed on the SAF population and will be presented by PH type and by age group. All summaries will be descriptive in nature. No statistical comparisons will be performed.

4.3.1.2.1 Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA v26.0 or higher. AEs will be classified as treatment-emergent for analysis in summary tables where applicable.

An overview summary of AEs, including number of event counts and percentages will be presented for participants with:

- any TEAEs,
- TEAEs related to study intervention,
- TEAEs leading to treatment discontinuation,
- Treatment-emergent SAEs,
- Treatment-emergent SAEs related to study treatment,
- TEAEs of special interest (i.e., injection site reactions; muscle pain or weakness; kidney stone events: renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring medication),
- Fatal TEAEs.

The number of events and number and percentage of participants with AEs will be summarized by SOC and PT. This summary will further be tabulated by strongest relationship to study intervention (related: definitely, probably, and possibly related; unrelated: unrelated; missing). A similar summary of TEAEs will be produced by maximum intensity (mild, moderate, severe, missing).

In addition, the number and percentage of participants who experienced (1) treatment-emergent SAEs; (2) TEAEs leading to study discontinuation; and (3) non-serious TEAEs (all TEAEs except serious TEAEs) that occurred in at least 2 or more participants will be presented by SOC and PT for SAF.

In addition, listings will be provided for TEAEs.

4.3.1.2.2 Clinical Laboratory Evaluations

Descriptive summaries for safety laboratory assessments will be presented at each visit starting at baseline. Changes from baseline to each post baseline visit will also be presented for continuous outcomes.

Baseline for safety laboratory assessments will be identified as defined in Section 4b.1.1.2 regardless of whether an evaluation was scheduled, retested, or unscheduled. Since laboratory retests can occur for individual parameters, it will be necessary to define the baseline and all subsequent visit-specific laboratory values individually for each parameter.

In the case where below the limit of quantitation (BLQ) results are observed, and the lower limit of quantification (LLOQ) value is known, the BLQ values will be included in the numeric summary as the reported LLOQ value. In for those lab results reported as '<x' where x is numeric value, descriptive summaries will impute x as the lab result.

The following imputation rules will be applied to safety laboratory results where LLOQ value is unknown:

- If the patient has quantifiable concentrations of that analyte from other study visits, BLQ results will be imputed as ½ of the patient's lowest concentration for that analyte.
- If the patient does NOT have any quantifiable concentrations of that analyte from other study visits, BLQ results will be imputed as ½ of the lowest concentration of that analyte based on all quantifiable results within the patient's age group.

By visit summary tables will be presented for each category of data separately. Routine clinical laboratory data will include hematology, clinical chemistry, coagulation parameters, and urinalysis.

Shift tables for baseline to maximum and minimum post baseline grades, based on laboratory normal ranges (below lower limit of normal [LLN], normal, above upper limit of normal [ULN]), will be provided for hematology, coagulation, cytokine, and clinical chemistry parameters. This analysis of extreme value shifts (e.g., maximum and minimum post baseline grades) will be based on all post baseline assessments whether scheduled or unscheduled.

Results of urine pregnancy tests (females only) will be presented in a listing only. Anti-drug antibody tests will be handled similarly.

Data listings for all laboratory results will be generated. Where appropriate, abnormal values (e.g., above the upper limit of normal or below the lower limit of normal) will be identified.

Participant data listings will include the type of visit (e.g., scheduled test, retest, unscheduled), age, sex, laboratory test, test units, laboratory test result, and the laboratory standard normal ranges adjusted as appropriate for age and sex, if available.

4.3.1.2.3 Vital Signs

Descriptive summaries for vital signs (systolic blood pressure, diastolic blood pressure, body temperature, pulse/heart rate, and respiration rate) will be presented for each visit starting at baseline (as defined in Section 4.1.1.2). Changes from baseline to each post baseline visit will also be presented.

Participant data listings of vital sign data will be provided.

4.3.1.2.4 Electrocardiograms

Electrocardiograms will be conducted at specific visits only. On Day 30, the ECGs will be conducted twice (pre-dose and 6 hours post dose).

All reporting for ECG data will be presented for central lab ECG results only. Descriptive summaries for ECG data (HR, PR interval, QRS duration, QT interval, corrected QT interval [QTcF, Fridericia correction], and RR) will be presented at each visit starting at baseline (defined in Section 4.1.1.2). Changes from baseline to each post baseline visit will also be presented.

If the RR is not collected it will be derived as follows: RR = (60/HR).

Change from baseline for QTcF and uncorrected QT will be classified as follows:

- ≤30 msec or >30 msec
- ≤60 msec or >60 msec

Absolute postbaseline QTcF and uncorrected QT interval will be classified as follows:

- ≤450 msec or >450 msec
- ≤480 msec or >480 msec
- ≤500 msec or >500 msec

Frequency counts and percentages will be tabulated for change from baseline and absolute post baseline QTcF values at each visit starting at baseline; participant listings will identify records where participant data falls into these regions. These summaries will also be presented for minimum and maximum post baseline values. The analysis of extreme values (e.g., maximum and minimum post baseline values) will be based on all post baseline assessments whether scheduled or unscheduled.

The number and percentage of participants with the following overall ECG results will also be tabulated at each visit. Shift tables for baseline to maximum post baseline overall ECG results, based on the three categories below will be provided. This analysis of extreme value shifts (e.g., maximum post baseline values) will be based on all post baseline assessments whether scheduled or unscheduled.

- Normal
- Abnormal, not clinically significant (NCS)
- Abnormal, clinically significant (CS)

All ECG data will be presented in data listings.

4.3.1.2.5 Physical Examination

Descriptive summaries for significant physical examination findings will be presented at each visit starting at baseline (as defined in Section 4.1.1.2). The supportive data listing of significant physical examination findings will be provided.

4.3.1.3 Secondary Endpoints in PK

The secondary endpoints in safety are listed below:

- Plasma PK parameters for nedosiran and/or its metabolites, including C_{max}, AUC_t and AUC_∞ (if estimable).

Pharmacokinetic parameters to be analysed will be described in detail in a separate pharmacokinetic analysis plan (PKAP).

4.4 Exploratory Endpoints Analyses

The exploratory efficacy endpoints listed below will be summarized for MITT population and by PH type and age group.

- The percent and absolute change from Baseline in plasma oxalate will be summarized (n, mean, standard deviation, median, minimum, maximum) by visit.
- The change from Baseline in annualized stone event rate will be summarized (n, mean, standard deviation, median, minimum, maximum).
- The change from Baseline in the PedsQL™ will be summarized (n, mean, standard deviation, median, minimum, maximum) by visit.
- The change from Baseline in the WPAI:PH, V2.0, CPV – Caregiver will be summarized (n, mean, standard deviation, median, minimum, maximum) by visit.

4.5 Other Safety Analyses

All safety analyses will be performed on the SAF population and will be presented by PH type and age group. All summaries will be descriptive in nature. No statistical comparisons will be performed.

4.5.1 Other Significant Adverse Events

Adverse events of special interest (AESI) will be summarized and include injection site reactions, muscle pain or weakness, and kidney stone events.

An injection site reaction is a disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. Potential ISRs will be graded as follows:

Individual signs or symptoms at the injection site (e.g., erythema, swelling, etc.) reported within 4 hours of study intervention administration will be recorded as AEs at injection site (not as an injection site reactions) and graded in accordance with the intensity categories.

At or after 4 hours post dose, signs or symptoms at the injection site will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 5.0) criteria for injection site reactions.

Injection site reactions and treatment-emergent signs of muscle weakness or pain will be summarized by SOC and PT. Summaries for these events by maximum severity will also be produced. However, only summaries by maximum intensity for injection site reactions ≥4 hours post dose will be based on CTCAE grading criteria (Grades 1 through 5; where Grade 1 is least severe, and Grade 5 is most severe) for injection site reactions. If a participant has both missing and non-missing CTCAE grades for a given SOC and PT, the missing CTCAE grade is selected for reporting unless the non-missing CTCAE grades is noted as Grade 4 or Grade 5. Kidney stone events will be summarized by the specific kidney stone event type that is collected on the adverse event CRF: renal stone requiring medical intervention, stone passage with or without hematuria, and renal colic requiring medication. Kidney stone events will also be summarized by maximum severity.

By-participant data listings for injection site reactions, treatment-emergent signs of muscle weakness or pain, and treatment-emergent kidney stones will be provided.

4.5.2 Echocardiogram with Doppler

Echocardiography will be performed at the Screening and final visits by a qualified sonographer/physician (and over-read by a cardiologist) using a standard, commercially available ultrasound machine. All echocardiogram data will be transmitted to a standalone imaging vendor, where qualified personnel will perform postprocessing of echocardiogram data and central over-read of all images. Only the central lab data will be reported. The report includes an overall assessment of cardiac anatomy, and quantitative evaluation of basic ventricular systolic function.

Descriptive statistics will be produced.

4.5.3 Concomitant Medication

Medications used at any time after the first dose date will be considered concomitant; this includes medications which initially start prior to the first dose date and continue during the posttreatment period, as well as new medications which are first recorded to have been taken after the first dose date. Missing medication start date handling will be based on the methodology described in Section 4.1.1.7. Medications will be coded using WHO-DD version March 2023 or later.

Concomitant medications will be summarized according to the anatomical therapeutic chemical (ATC) level-2 class and ATC level-4 class. To count the number of participants who took a medication, a participant taking the same medication multiple times will only be counted once for that medication. Medication use will be tabulated in decreasing order of the overall number of participants who took each medication. In addition, the total number of participants to ever take any concomitant medications will be presented.

Participant medication data will be presented in data listings.

4.5.4 Immunogenicity Assessments

Participant anti-drug antibody testing results will be presented in a data listing. Participant antibody testing results will be presented in a data listing.

4.6 Other Analyses

4.6.1 Exposure and Compliance

Summary statistics of the number of doses received, the number of participants who received study intervention for each dosing visit, and the percent of scheduled doses received will be presented. All the tabulations will be for SAF.

All study intervention administration information will be presented in participant data listings.

4.6.2 Fluid Intake

All fluid intake information will be presented in a data listing for SAF.

4.7 Interim Analysis

Interim analysis will be conducted when first 15 PH1 participants complete the study. The interim analysis will include efficacy data of participants in the Interim Analysis Population and safety data of participants in the Safety Analysis Population with age of 2-11 years.

The Sponsor reserves the right to conduct additional interim analyses if needed to support regulatory activities.

4.8 Changes to Protocol-planned Analyses

Not applicable.

5 Sample size determination

It is expected that approximately 25 participants will be screened, such that approximately 20 participants will complete the Day 180 assessments.

No formal sample size estimations were performed. A sample size of 20 participants was considered sufficient to provide an initial assessment of the efficacy and safety of nedosiran in paediatric participants (birth to 11 years of age) with PH1, PH2 or PH3 and relatively intact renal function.

6 References

1. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916;17:863–71.

2. Schwartz G.J., Schneider M.F., Maier P.S., Moxey-Mims M., Dharnidharka V.R., Warady B.A. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int.* 2012 Aug 2;82(4):445-53.

3. Uemura O, Nagai T, Ishikura K, Ito S, Hataya H, Gotoh Y, et al. Creatinine-based equation to estimate the glomerular filtration rate in Japanese children and adolescents with chronic kidney disease. Clin Exp Nephrol. 2014a;18(4):626–33.

4. Uemura O, Nagai T, Ishikura K, Ito S, Hataya H, Gotoh Y, et al. Cystatin C-based equation for estimating glomerular filtration rate in Japanese children and adolescents. Clin Exp Nephrol. 2014b;18(5):718-25.

5. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. Medical Care. 2001 Aug 1:800–12.

6. Varni JW, Seid M, Rode CA. The PedsQL™: Measurement model for the Pediatric Quality of Life Inventory™. Medical Care. 1998;37:126–39.

7. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL™ family impact module: preliminary reliability and validity. Health Qual Life Outcomes. 2004 Dec;2(1):55.

8. Rijnbeek, P. R., et al. New normal limits for the paediatric electrocardiogram. Eur Heart J 2001 22(8): 702-711.