Cover Page for Protocol

Sponsor name:	Dicerna Pharmaceuticals, Inc., a wholly owned subsidiary of Novo Nordisk
NCT number:	NCT05001269
Sponsor trial ID:	DCR-PHXC-203
Official title of study:	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
Document date:*	23-February-2023

*Document date refers to the date on which the document was most recently updated.

Redacted protocol
Includes redaction of personal identifiable information only.

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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**
Protocol Number:	DCR-PHXC-203
Compound:	Nedosiran, also known as DCR-PHXC
Study Phase:	2
Short Title:	Nedosiran in Pediatric Patients from Birth to 11 Years of Age with PH1, PH2, or PH3 and Relatively Intact Renal Function
Acronym:	PHYOX8
EudraCT Number:	2021-001083-16
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Sponsor Name:	Dicerna Pharmaceuticals, Inc. 75 Hayden Ave. Lexington, MA 02421 US (617) 621-8097

Version History:	Amendment 3 (version 4.0)	23-Feb-2023
	Amendment 2 (version 3.0)	01-Nov-2022
	Amendment 1 (version 2.0)	21-Dec-2021
	Original Protocol (version 1.0)	15-Apr-2021

Sponsor Signature Page

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 Number: DCR-PHXC-203

Version: 4.0
Date: 23-Feb-2023

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[redacted], MD, PhD Date
[redacted]
Novo Nordisk A/S

[redacted] 24-Feb-2023

[redacted], MBA, RAC Date
[redacted] Regulatory Affairs
Dicerna Pharmaceuticals, Inc.

[redacted] 24-Feb-2023

[redacted], MS Date
[redacted], Biostatistics
Dicerna Pharmaceuticals, Inc.

Medical Monitor and Pharmacovigilance Contact Information

SAE Submission Coordinator:

Novo Nordisk Safety Operations

24-hour Safety Fax: +45 44427787

Email: soclin@novonordisk.com

Clinical Research Organization Medical Monitor:

Premier Clinical Research

3800 Paramount Parkway, Suite 400

Morrisville, NC 27560-6949

24-hour emergency telephone: +44 118 936 4096

+1 512 686 1256

Email: 203_DCR-PHXC_MedicalMonitors@premier-research.com

Sponsor Medical Monitor:

Dicerna Pharmaceuticals, Inc.

Telephone +1 617 621 8097

Email: PHYOX8medicalmonitors@dicerna.com

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3, version 4.0	23-Feb-2023
Amendment 2, version 3.0	01-Nov-2022
Amendment 1, version 2.0	21-Dec-2021
Original Protocol, version 1.0	15-Apr-2021

Amendment 3, version 4.0 (23-Feb-2023)

The 01-Nov-2022 version of the protocol was amended to provide for inclusion of participants weighing less than 10 kg. Additional updates and clarifications were also included. The table below details the summary of changes.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Removed the 10 kg minimum body weight from the inclusion criteria.	To align with the 0- to 1-year-old age group that is included in this study.
2.3.4 Risk Management 8.2.6 Clinical Safety Laboratory Assessments 10.3 Appendix 3 (new section)	Added text regarding maximum blood volume collection allowed based on body weight and to direct the Investigator to the Laboratory Manual for the blood draw priority list.	To provide guidance around maximum allowable blood volume collection in pediatric patients for whom a full collection of blood would exceed allowable limits
1.1 Synopsis 4.1 Overall Design	Updated study duration from 18 to 24 months.	To account for enrollment delays.
1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design	Updated timeframe for repeat screening laboratory assessments.	To expand the allowable timeframe from 7 to 14 days to account for technical or logistic issues at the central lab.
5.1 Inclusion Criteria 6.5 Concomitant Therapy	Added text to allow for interval weight gain dose adjustments in concomitant therapy regimens.	To clarify that dose adjustment based on interval weight gain is not considered a change in dose regimen.
1.3 Schedule of Activities 8.1.5 Reporting Fluid Intake	Updated text to clarify the range of 4 to 7 days for reporting of fluid intake.	To clarify that it is preferred for daily fluid intake to be reported for all 7 days prior to each urine collection period, and if not possible, intake for at least the 4 days prior to collection will be reported.
1.3 Schedule of Activities	Updated footnote aa to specify the ages of patients requiring PedsQL to be provided by parental proxy.	To update that patients aged birth to 12 months and 13 to 24 months will have information provided by parental proxy.
8.1.1 Spot Urine Collection	Added text regarding spot urine collection in infants.	To clarify that instructions for spot urine collection in infants are also provided in the Urine Collections Instructions.
2.2.3.1 Clinical Studies of Nedosiran	Added additional text denoting differences in response between participants with PH1 and PH2 in study DCR-PHXC-201.	To clarify that participants with PH2 did not have a response equivalent to that of those with PH1.
Sponsor Signature Page	Updated current signatory titles/information for accuracy.	To account for Sponsor signatory corrections.
Medical Monitor and Pharmacovigilance Contact Information	Updated with current personnel contact information.	To account for Sponsor contact changes.
Throughout protocol	Minor text updates and grammatical changes	For increased clarity.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: Nedosiran in Pediatric Patients from Birth to 11 Years of Age with PH and Relatively Intact Renal Function

Acronym: PHYOX8

Study Rationale:

This study is designed to evaluate the efficacy, safety, and PK of nedosiran in neonates, infants, and children (birth to 11 years of age) with primary hyperoxaluria (type 1 [PH1], type 2 [PH2], and type 3 [PH3]) and relatively intact renal function based upon eGFR and serum creatinine.

There are 3 types of PH (PH1, PH2, and PH3); each is attributed to a specific gene mutation. Overproduction of oxalate in the liver is a prominent observation in all 3 types of PH. As a genetic disease, the clinical manifestations of this excess oxalate burden start building early in life. The median age of symptom onset for individuals with PH is 4.5 years. It is therefore important to study the safety and efficacy of nedosiran in the youngest children, before late complications of the disease have developed.

Nedosiran, a synthetic RNAi drug that consists of a double-stranded oligonucleotide conjugated to GalNAc ligands, is designed to substantially reduce the activity of a key oxalate-producing enzyme. The potential medical value of achieving a sustained substantial decrease and/or normalization of liver oxalate production in patients with PH is demonstrated by the marked improvement in disease outcome in patients with PH1 in whom liver oxalate production has been reduced to normal levels by liver transplantation.

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 Quality of Life (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 intact renal function based upon eGFR and serum creatinine	• Change from Baseline in the Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0, Clinical Practice Version (WPAI:PH, V2.0, CPV) – Caregiver in PH1, PH2, or PH3 participant subgroups

Overall Design

This is a Phase 2, multi-dose (3.5 mg/kg, not to exceed 170 mg), open-label, single-arm, uncontrolled, multicenter study of nedosiran in pediatric participants (birth to 11 years of age)

with genetically confirmed PH type 1 (PH1), type 2 (PH2), or type 3 (PH3) with relatively intact renal function based upon eGFR and serum creatinine.

Participants will receive monthly SC doses (3.5 mg/kg, not to exceed 170 mg) of nedosiran over 6 months.

The primary objective of this study is to characterize the efficacy of nedosiran in pediatric participants (birth to 11 years of age) with PH1, PH2, or PH3. The efficacy of nedosiran in lowering Uox will be assessed via monthly spot urine samples.

Participants completing this study may be eligible for long-term treatment with nedosiran in Study DCR-PHXC-301.

Disclosure Statement: This is a sequential-group, open-label treatment study with no masking.

Study Population:

Male and female pediatric participants (birth to 11 years of age), with genetically confirmed PH1, PH2, or PH3, and relatively intact renal function based upon eGFR and serum creatinine.

Key inclusion criteria include

- Estimated glomerular filtration rate (eGFR) at Screening ≥ 30 mL/min normalized to 1.73 m^2 body surface area (BSA). For infants aged less than 12 months, serum creatinine below the 97.5th percentile of a healthy population (Boer et al., 2010).
- Average spot Uox-to-creatinine ratio at Screening above 2 times the 95th percentile for age based on Matos et al, 1999:
  - > 0.44 mol/mol in participants < 6 months
  - > 0.34 mol/mol in participants from 6 months to <12 months
  - > 0.26 mol/mol in participants 12 months to < 2 years
  - > 0.20 mol/mol in participants from 2 to < 3 years and
  - > 0.16 mol/mol in participants from 3 to < 5 years
  - > 0.14 mol/mol in participants from 5 to < 7 years
  - > 0.12 mol/mol in participants from 7 to 11 years

Key exclusion criteria include

- Renal or hepatic transplantation (prior or planned within the study period)
- Plasma oxalate (Pox) > 30 µmol/L at Screening
- Documented evidence of clinical manifestations of severe systemic oxalosis (including preexisting retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations)

Number of Participants: Approximately 25 participants will be enrolled such that approximately 20 participants (approximately 7 aged 6 to 11 years; approximately 10 aged 1 to

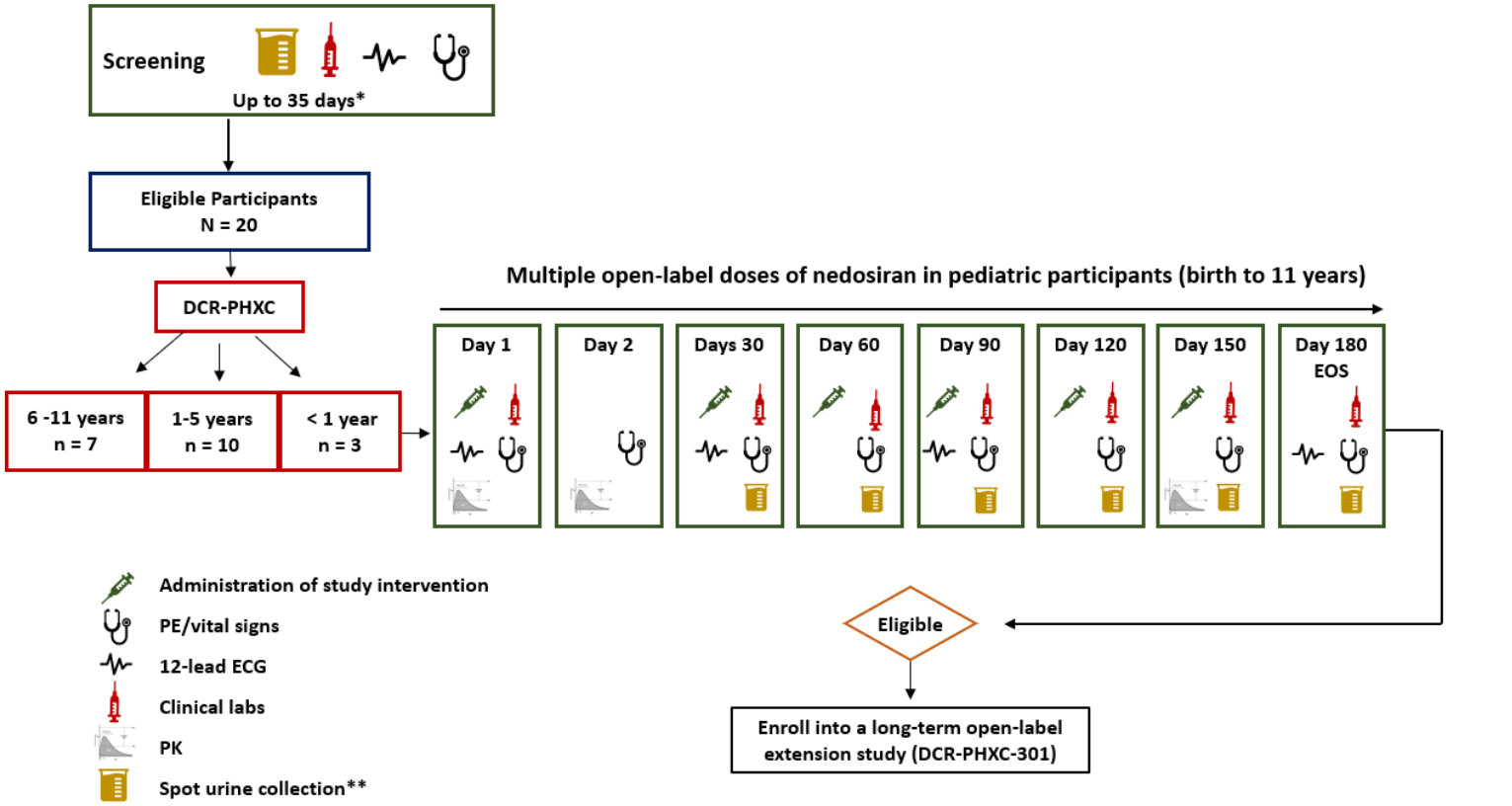
5 years; and approximately 3 aged < 1 year) complete the study, with an overall goal of approximately 15 PH1.

Intervention Groups and Duration of Participation: This study has a single intervention group in which all participants will receive monthly SC doses of nedosiran over a 6-month period. Prospective participants will be screened over an up-to-35-day period, with an extra 14 days allowed for participants who are required to repeat initially unanalyzable screening laboratory assessment samples. The total time on study for each participant is approximately 7 months.

Study Duration: Approximately 24 months from the first participant, first visit, to the last participant, last visit.

Safety Review Committee: This study will utilize an SRC to review safety and efficacy data on a periodic basis.

1.2. Schema



* An extra 14-day period will also be granted for participants who are required to repeat initially unanalyzable screening laboratory assessment samples or where lab samples are delayed due to technical/logistical issues at the central lab.
**Spot urine collection will include 6 samples at Screening and 4 samples at all other time points indicated in the schema

1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Day (window)	**Screening**	**Treatment**									**EOS**	**ET**
	–35 [a] to –1	**1 [b]**	**2**	**15**	**30 (±2)**	**45**	**60 (±3)**	**90 (±3)**	**120 (±5)**	**150 (±5)**	**180 (±5)**	**-**
At-clinic visit	**X**	**X**			**X**			**X**			**X**	
At-home telehealth visit [c]			**X**				**X**		**X**	**X**		
Telephone Contact [d]				**X**		**X**						
Procedure/Assessment												
Study intervention administration [e]		X			X		X	X	X	X		
Informed consent [f]	X											
Inclusion/exclusion criteria [g]	X	X										
Demographic/baseline characteristics	X											
Medical history	X											
PH disease history [h]	X											
Medication history [i]	X											
PH genotyping [j]	X											
Plasma oxalate sample	X										X	X
Spot urine collection [k]	X				X		X	X	X	X	X	X
Plasma PK sample [l]		X	X		X			X		X		X
Record fluid intake [m]	X				X		X	X	X	X	X	X
12-lead ECG [n]	X	X			X			X			X	X
Vital signs [o]	X	X	X		X		X	X	X	X	X	X
Physical examination [p]	X	X	X		X		X	X	X	X	X	X
Height and body weight [q]	X	X			X			X			X	X
Hematology [r]	X	X			X			X			X	X
Chemistry [r]	X	X			X		X	X	X	X	X	X
Coagulation [s]	X	X			X			X			X	X
eGFR [t]	X	X			X		X	X	X	X	X	X
Urinalysis [u]	X	X			X		X	X	X	X	X	X
Urine pregnancy test (WOCBP) [v]	X	X			X		X	X	X	X	X	X
Record stone events [w]		X	X		X		X	X	X	X	X	X
Kidney ultrasound [x]	X										X	X
Echocardiogram [y]	X										X	X
ADA sample	X				X			X		X	X	X

Study Day (window)	**Screening**	**Treatment**									**EOS**	**ET**
	–35 [a] to –1	**1[b]**	**2**	**15**	**30 (±2)**	**45**	**60 (±3)**	**90 (±3)**	**120 (±5)**	**150 (±5)**	**180 (±5)**	**-**
At-clinic visit	**X**	**X**			**X**			**X**			**X**	
At-home telehealth visit [c]			**X**				**X**		**X**	**X**		
Telephone Contact [d]				**X**		**X**						
Procedure/Assessment												
Pediatric burden assessment [z]		X			X		X	X	X	X	X	X
PedsQL [aa]	X										X	X
Pharmacoeconomics [bb]	X							X			X	X
Record AEs and SAEs [cc]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [i]		X	X		X		X	X	X	X	X	X

[a] An extra 14-day period will also be granted for participants who are required to repeat initially unanalyzable screening laboratory assessment samples or where lab samples are delayed due to technical/logistical issues at the central lab.

[b] In order to minimize blood loss in participants, samples to be drawn for screening should be collected not less than 28 days prior to samples drawn on Day 1.

[c] Visits for Days 2, 60, 120, and 150 may be conducted at the clinic or as at-home telehealth visits. During at-home telehealth visits, home-health nurses will collect the required blood and urine samples and perform an assessment of vital signs. The Investigator will contact the participant's caregiver via telephone and/or video conference to assess the general well-being of the participant and determine if any adverse events have occurred. The Investigator must affirm that nedosiran may be administered prior to administration.

[d] The Investigator will contact the participant's caregiver via telephone and/or video conference to assess the general well-being of the participant and determine if any adverse events have occurred.

[e] After the first 2 injections of nedosiran, visiting nurses or caregivers will administer SC injections at home for those months at which a study-site visit is not required. The total dose will be based upon body weight recorded on study Day 1. For participants < 6 months of age at Screening, the dose will be adjusted at Day 90 to capture changes in weight; no other dose adjustments are allowed.

[f] Parental informed consent (and minor assent, if applicable per local regulations) is required prior to initiation of screening procedures.

[g] Participant eligibility (with the exception of clinical laboratory testing) will be re-confirmed prior to administration of study intervention on Day 1.

[h] PH history to include 12-month history of stone events, or as applicable for those less than 12 months of age (Section 8.1.3).

[i] To include vitamin B6 (pyridoxine), if applicable.

[j] Participants without documented genotyping must provide a DNA sample for testing. For participants who weigh ≤ 11 kg, PH genotyping will be performed via buccal swab; for all other participants, while genotyping via buccal swab is recommended to reduce blood sample volumes, genotyping performed via whole blood sample is allowed.

[k] Spot urine samples will be collected for the determination of Uox and urinary creatinine. At screening, 6 spot urine samples (3 of which must be second morning voids) will be collected over a 3-day period. On-treatment, 4 spot urine samples (2 of which must be second morning voids) will be collected over a 2-day period on a monthly basis.

[l] Plasma sampling times for PK analysis (see Section 8.5):

Sampling times:	Allowable Windows:
Day 1: one sample in the 0- to 4-hour postdose window and one sample in the 4- to 24-hour postdose window Days 2, 30, and 90: one single sample during the visit Day 150: predose, one sample in the 0- to 4-hour postdose window, and one sample in the 4- to 24-hour postdose window	Predose: within 30 minutes before administration of study intervention Not applicable for other samples

A single plasma sample should be collected at the final visit from participants who discontinue study intervention or are withdrawn from the study. When multiple assessments are due at the same time point, PK sampling should be performed at the nominal time point, with the preferred order of assessments ECG, vital signs, PK, and then other assessments.

[m] Participants should maintain consistent fluid intake (i.e., hyperhydration) over the course of the study (Section 5.3). Participants' caregivers will report daily fluid intake over the week prior to each urine collection period (Section 8.1.5). Recording of fluid intake only applies to non-breastfed participants.

[n] On Days 1 and 30, ECG to be performed predose and at 6 hours postdose. A single ECG to be performed at other visits, as indicated (Section 8.2.4). A ± 30-minute window is allowed if multiple assessments are due at the same time point.

[o] Vital signs on Day 1 and Day 30 to be assessed predose and at 6 hours postdose (Section 8.2.3). A ± 30-minute window is allowed if multiple assessments are due at the same time point. In such cases, PK sampling should be performed, preferably at the nominal time point, with the preferred order of assessments ECG, vitals, PK, and then other assessments.

[p] Physical examination includes height/length, weight, inspection of injection site(s), and review of body systems. A full physical exam will be performed at Screening and Day 180 (or early termination). For at-home visits, the home-health nurse will provide in-person support to the Investigator in assessing the participant; height and weight will not be measured during at-home visits. The physical examination performed at other scheduled visits (Days 1 through Day 150) or unscheduled visits may be a brief or full physical examination at the Investigator's discretion. See Section 8.2.1 and Section 8.2.2.

[q] The total dose will be based upon body weight recorded on study Day 1. For participants < 6 months of age at Screening, the dose will be adjusted at Day 90 to capture changes in weight; no other dose adjustments are allowed.

[r] Blood samples for hematology and serum chemistry to be collected predose on dosing days. A single blood draw to be performed at other visits, as indicated. See Section 10.2 for the list of parameters.

[s] Blood samples for coagulation studies to be collected predose. Coagulation panel will include prothrombin time (PT) and international normalized ratio (INR). Additional coagulation studies may be performed as clinically indicated.

[t] Estimated glomerular filtration rate (eGFR) to be calculated only in participants aged 12 months and older, as described in Section 8.2.6.1.

[u] Urinalysis with microscopy at Screening and as clinically indicated. Dipstick urinalysis may be performed at other scheduled visits. Collect sample for urinalysis before dosing. See Section 10.2 for parameters.

[v] A positive urine pregnancy test will be confirmed with a serum pregnancy test. Administration of study intervention will be discontinued in any participant with a positive pregnancy test. A final pregnancy test will be conducted 2-3 weeks following the last dose of study intervention in any WOCBP who prematurely discontinues the study.

[w] Parent(s)/legal guardian will report instances of renal stones requiring medical intervention, stone passage, and/or renal colic requiring medication (Section 8.1.3.1).

[x] In the event of rescreening, if a participant had been screened for this study within the last 3 months and had ultrasound data sent to the central over-readers, repeat of the ultrasound will not be required during the rescreen.

[y] For an individual participant, if the echocardiogram cannot be performed without sedation (e.g., due to age), the echocardiogram should not be performed. The omission of an echocardiogram due to sedation requirement should not be considered a protocol deviation. In the event of rescreening, if a participant had been screened for this study within the last 3 months and had echocardiogram data sent to the central over-readers, repeat of the echocardiogram will not be required during the rescreen.

[z] Participants or parent(s)/legal guardian to be queried as to the ongoing burden of the study (Section 2.3.2).

[aa] For participants aged birth to 12 months, 13 to 24 months, 2 to 5 years, 5 to 7 years, and 8 to 11 years, the Peds QL will be completed by parental proxy, and the PedsQL family module will be completed for all participants (Section 8.1.4).

[bb] To include medical resource utilization questions and the WPAI:PH V2.0 CPV, both to be completed by the parent/guardian (Section 8.10).

[cc] Adverse events to be collected from the time of ICF signature through the End of Study/Early Termination Visit. Serious adverse events to be collected from the time of ICF signature through 30 days after the after last day of study participation.

2. INTRODUCTION

Nedosiran (also known as DCR-PHXC) is a synthetic RNAi drug that consists of a double-stranded oligonucleotide conjugated to GalNAc ligands that is being developed for treatment of primary hyperoxaluria (PH).

2.1. Study Rationale

Primary hyperoxaluria encompasses 3 genetically distinct, autosomal-recessive, inborn errors of glyoxylate metabolism characterized by the over-production of oxalate, a highly insoluble metabolic end product that is eliminated mainly by the kidney. Patients with PH are predisposed to the development of multiple and recurrent urinary tract (urolithiasis) and kidney (nephrolithiasis) stones. Calculi formation is accompanied by nephrocalcinosis in some patients with PH. This deposition of calcium oxalate in the renal parenchyma produces tubular toxicity and renal damage that is compounded by the effects of renal calculi-related obstruction and frequent superimposed infections (Cochat & Rumsby, 2013).

Primary hyperoxaluria is present at birth and although first symptoms might occur at different ages, the excess oxalate burden starts building early in life. It will therefore be important to reduce Uox concentrations as soon as the diagnosis of PH is being made to avoid deterioration of renal function. According to data from the Rare Kidney Stone Consortium, median age of symptoms for PH patients is 4.5 years and median age of diagnosis is 8.1 years (Zhao et al., 2016). European Society of Pediatric Nephrology and European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry show that children less than 2 years of age with infantile oxalosis had a higher risk of death (a HR, 3.44; 95% CI, 1.15–10.28; P=0.02) compared with patients with PH aged greater than 2 years with renal replacement therapy (Harambat et al. 2012). It is therefore important to study the safety and efficacy of nedosiran in the youngest children, before complications of the disease have developed.

At present, one treatment for PH1, Oxlumo™ (lumasiran, Alnylam), is approved in a limited number of countries, including the European Union. There is an unmet need for treatment in all subtypes of PH globally and particularly for PH2 and PH3, as no therapies are presently approved by regulatory authorities for the treatment of patients with PH2 or PH3. When treatment is not available, a number of supportive therapies are used in an attempt to mitigate some of the effects of the disease. These interventions are burdensome to the patient and their caregivers and are not highly effective at preventing progression of disease.

The Sponsor is developing nedosiran (also known as DCR-PHXC) as a treatment for PH that is intended to prevent the enzymatic conversion in the liver of glyoxylate to oxalate, which should block the production of oxalate in the liver in all genetic forms of PH (PH1, PH2, and PH3). This effect has been demonstrated in nonclinical studies. A study in adolescent and adult participants with PH1 and PH2 (DCR-PHXC-201) demonstrated that DCR-PHXC was generally well tolerated and safe in patients with PH1 and PH2 with intact renal function. DCR-PHXC demonstrated efficacy by significantly lowering Uox in participants with PH1, however efficacy results were inconclusive for participants with PH2.

This study is being conducted to assess the effect of nedosiran on Uox excretion in pediatric participants (birth to 11 years of age) with PH1, PH2, or PH3.

2.2. Background

2.2.1. Overview of Primary Hyperoxaluria

Primary hyperoxaluria encompasses 4 related rare diseases, 3 of which are attributed to mutations in specific genes (PH1, PH2, and PH3) and a fourth for which there is currently no identified genetic cause (no-mutation-detected primary hyperoxaluria, known as NMD-PH).

Primary hyperoxaluria is a devastating disease that presents across the age continuum with a broad range of medically important abnormalities (Cochat & Rumsby, 2013). As a genetic disease, PH is present at birth but manifestations can occur at any time. All 3 genetic forms of PH exhibit some extent of overlap in the clinical manifestations, where overproduction of oxalate is a prominent observation (Hoppe, 2012; Hoppe et al., 2009). Presenting symptoms from early childhood through adolescence are most often related to kidney stone disease, including hematuria, dysuria, pain, urinary tract infection, or stone passage (Hoppe et al., 2009). Initial symptoms occur in most individuals before the age of 10 years, and in 85% to 90% by age 20 years (Hoppe et al., 2009; van der Hoeven et al., 2012; Mandrile et al., 2014). Renal oxalate deposition in patients with PH1 and some patients with PH2 and PH3 leads to nephrocalcinosis, tubular dysfunction, and progression to ESRD. Systemic oxalosis occurs in patients with PH1 and some patients with PH2 and PH3 due to the over-production of oxalate by the liver and the impairment of the body's ability to eliminate oxalate, producing a broad range of serious life-threatening complications (Hoppe et al., 2021). The consequences of systemic deposition of calcium oxalate crystals in patients with systemic oxalosis include fracturing bone disease, nonhealing painful cutaneous ulcers, treatment-refractory anemia, retinal calcium oxalate deposition, and cardiomyopathy and arrhythmias due to deposition in the cardiac conduction system (Hoppe et al., 2009).

A review of 330 patients with PH1 demonstrated that the outlook for these patients without treatment is poor, with ESRD present in 50% of patients by the age of 15 years and in 80% by the third decade (Latta & Brodehl, 1990). Although early initiation of aggressive conservative treatment (high fluid intake, inhibitor of calcium oxalate crystallization, and pyridoxine in responsive cases) can help slow or delay progression to ESRD, there is still substantial morbidity across the age continuum. In one study of 78 infants with PH1, 33 underwent kidney, liver, or kidney-liver transplantation. The age at first transplantation was 6.4 ± 7.8 years (Cochat et al., 1999). Fifty-two percent of these patients died.

Primary hyperoxaluria type 2 was first described in 1968 based on the absence of glycolate and the presence of L-glyceric acid in the urine from 4 cases with hyperoxaluria (Williams & Smith, 1968). Primary hyperoxaluria type 2 is much rarer than PH1 and is characterized by recurrent nephrolithiasis with nephrocalcinosis. A recent study of 101 patients with PH2 suggested that PH2 patients are at a much higher risk than previously anticipated to develop CKD (in ~50% of patients) and ESRD (in ~25% of patients) (Garrelfs et al., 2019).

Lumasiran is approved in a limited number of countries, including the European Union as a treatment for PH1. Lumasiran reduces levels of glycolate oxidase (GO) enzyme, which only has an effect on PH1, and therefore is not a viable treatment for PH2 or PH3 (Oxlumo™ [lumasiran, Alnylam] Highlights of Prescribing information, 2020). For patients without a treatment option, a number of supportive therapies are used in an attempt to mitigate some of the effects of the disease. Current medical management before renal failure develops is underpinned by

hyperhydration, with fluid intake recommendations of at least 3 liters per day per square meter of body-surface area (5 L/day for a 70-kg adult) (Cochat et al., 2012). These regimens can be problematic in infants and toddlers, necessitating placement of a gastrostomy tube to ensure adequate nighttime fluid administration. Affected patients are at considerable risk of serious complications during periods of increased fluid loss (fever, diarrhea/vomiting, and urinary tract infections) or when oral hydration is compromised (following surgical procedures). Oral potassium citrate administration is used to inhibit crystallization and alkalinize the urine. Treatment with vitamin B6 is effective in decreasing Uox in approximately 10% to 30% of patients with PH1 with certain *AGXT* mutations but has not been proven effective in treating other forms of PH (Salido et al., 2012; Hoppe et al, 2009; Hoyer-Kuhn et al., 2014).

For patients with more advanced disease, dialysis may be used in an attempt to remove endogenously over-produced oxalate. In contrast to the more typical 3-times-weekly hemodialysis regimens used in other types of renal failure, patients with PH may require hemodialysis 6 or 7 days per week. Given the limitations of dialysis and the inability to substantially impact oxalate over-production in most patients with PH1, most centers now consider liver transplantation approaches earlier in the disease course to minimize the risk of irreversible tissue damage.

Other treatments include renal transplantation or combined liver and kidney transplantation (Nolkemper et al., 2000; Rogers et al., 2001; Dhondup et al, 2018; Del Bello et al., 2020). As with organ transplantation in other diseases, these procedures are associated with significant medical risk and a requirement for long-term treatment with immunosuppressive drugs that are also associated with significant side effects.

2.2.2. Nonclinical Overview

Nedosiran consists of the drug substance, nedosiran sodium (also known as DCR-L1360) in WFI. Nedosiran sodium is a synthetic double-stranded (hybridized duplex) RNA oligonucleotide conjugated to GalNAc aminosugar residues. After SC administration, the GalNAc sugars conjugated to the RNA oligonucleotide bind to ASGPR to deliver nedosiran sodium to hepatocytes. Nedosiran sodium reduces the level of mRNA encoding the dominant form of the LDH enzyme, specifically, the LDHA isoenzyme. Lactate dehydrogenase catalyzes the cytosolic conversion of glyoxylate to oxalate in the liver and this biochemical reaction is believed to be critical for oxalate generation for all 3 genetic forms of PH.

Inhibition of oxalate production has been accomplished in mouse models of PH1 and PH2 and in an indirect mouse model of PH3.

Nedosiran sodium was not associated with any adverse effects on cardiovascular, respiratory, or neurological function in cynomolgus monkeys when administered as a single SC injection at doses up to 300 mg/kg. In addition, in the pivotal repeat-dose toxicity studies (up to 6 months in mice and up to 9 months in monkeys), nedosiran sodium was well tolerated at dose levels up to 300 mg/kg in both mice and monkeys.

In definitive GLP fertility and early embryonic development and EFD studies in mice, no test-article-related toxicity was observed at dose levels up to 2000 mg/kg nedosiran sodium (highest dose administered) or 10 mg/kg of the mouse analog. In a preliminary, non-GLP, EFD study in rabbits (dose levels: 20 to 600 mg/kg), lower body weight gains in dams (with accompanying

lower food consumption) and embryofetal effects (higher litter proportions of postimplantation loss and lower numbers of live fetuses) were observed from the lowest doses. In addition, increased incidences of cardiovascular fetal malformations were noted. The human relevance of these contradictory observations in mice and rabbits is unclear, as nedosiran is not pharmacologically active in rabbits (i.e., no *Ldha* knockdown) and no such observations were noted in the mouse EFD studies with nedosiran or the pharmacologically active mouse analog.

See the Nedosiran IB for more details on the nonclinical studies.

2.2.3. Clinical Overview

2.2.3.1. Clinical Studies of Nedosiran

Nedosiran is being evaluated for the treatment of adults and children with PH in a series of completed and ongoing studies.

Study DCR-PHXC-101 was a single ascending dose study conducted to evaluate the safety, tolerability, PK, and PD of nedosiran in healthy volunteers and participants with PH1 and PH2. A total of 33 participants (15 healthy volunteers and 18 participants with PH [including 3 adolescents]) received a single dose of nedosiran. Nedosiran was generally safe and well tolerated in healthy volunteers and participants with PH1 and PH2. No treatment- or dose-related trends in the frequency, severity, or relatedness of TEAEs were observed. Injection site reactions were reported in 13.3% of healthy volunteers and 27.8% of participants with PH receiving nedosiran. Treatment-emergent SAEs were reported in 4 participants (22.2%); no SAEs were considered treatment-related. No clinically significant changes in cytokine levels were reported for the participants experiencing ISRs. A single-dose administration of nedosiran produced clinically meaningful reductions in 24-hour Uox in participants with PH1 and PH2. The mean maximum percent reduction in 24-hour Uox across cohorts was 64% (range 28%-100%), with a dose-response trend observed. Normalization of Uox (defined as Uox excretion < 0.46mmol/24 hours) was achieved in 10 of 18 participants with PH1 or PH2, with an additional 4 participants achieving near-normalization (defined as Uox excretion 0.46 to < 0.60 mmol/24 hours).

Study DCR-PHXC-201 was a multicenter, randomized, placebo-controlled study designed to evaluate the efficacy and safety of nedosiran over a 6-month treatment period in participants with PH1 and PH2). A total of 35 participants were randomized and received treatment: 23 to nedosiran and 12 to placebo; of these, 33 completed study treatment and continued onto the extension study, Study DCR-PHXC-301.

The primary objective of the study was met with strong statistical significance. The reduction of 24-hour Uox, measured as the $AUC_{24\text{-hour Uox}}$, from Day 90 to Day 180 in the nedosiran group was significantly greater than that in the placebo group ($P < 0.0001$). The key secondary efficacy endpoint analysis confirmed the primary endpoint analysis, as a significantly greater percentage of participants in the nedosiran group (50%) achieved normalization or near-normalization of 24-hour Uox on at least 2 consecutive visits starting at Day 90 compared to placebo (0; $P = 0.0025$). When results were broken down by PH type, participants with PH1 demonstrated a significant reduction in 24-hour Uox from Baseline in the nedosiran group compared to the placebo group. ANCOVA modeling was not possible in participants with PH2; however,

individual participant observation did not show a consistent reduction of 24-hour Uox in participants with PH2 receiving nedosiran.

Nedosiran was generally safe and well tolerated. The majority of TEAEs were mild or moderate in severity. Treatment-related TEAEs occurring in more than 1 nedosiran participant and more frequently in the nedosiran group than the placebo group were injection site erythema and injection site pain. A total of 8.7% of participants in the nedosiran group experienced ISRs. All ISRs were CTCAE Grade 1 and all resolved by the end of the study. SAEs were reported by 1 nedosiran participant and 2 placebo participants. The participant in the nedosiran group experienced an SAE of tachycardia considered by the Investigator to be possibly related to treatment due to the temporal relationship of the event to study drug exposure. The participant was withdrawn from treatment due to the tachycardia. Based upon external expert review of the case, the Sponsor assessed the event as not related. No trends indicative of clinically important effects of nedosiran on laboratory or other clinical parameters were observed. No new risks were identified.

Study DCR-PHXC-104 was a multicenter, Phase 1, randomized, placebo-controlled, double-blind, single-dose trial of nedosiran in patients with PH3. The primary objective was to evaluate the safety profile of nedosiran in patients with PH3. The secondary objectives were to characterize the plasma PK of nedosiran and to determine the effect of nedosiran in lowering Uox after single-dose administration in patients with PH3. Six participants were randomized: 4 to nedosiran and 2 to placebo; all 6 randomized participants received one dose of study drug and completed the study.

Overall, nedosiran was well tolerated. All TEAEs were mild in severity. No TEAEs were considered serious or treatment related and no participant was withdrawn from the study due to a TEAE. There were no treatment-related trends in vital sign, physical examination, or ECG data observed between the nedosiran and placebo groups.

The efficacy endpoint was not met, as no participants achieved a > 30% decrease from baseline in 24-hour Uox on 2 consecutive visits. However, at Day 85, all participants in the nedosiran group experienced decreases in 24-hour Uox from Baseline, with a mean decrease of 24.5%. Two participants in the nedosiran had greater than 30% decreases in 24-hour Uox at a single visit. Similar trends were not observed in the 2 placebo-arm participants. As such, further evaluation of the efficacy of nedosiran in participants with PH3 is warranted.

Studies DCR-PHXC-301 (long-term roll-over study in patients with PH1, PH2, or PH3) and DCR-PHXC-204 (a 6-month open-label study in patients with severe renal impairment or ESRD) are ongoing. Both studies include participants < 18 years of age.

Nedosiran has an acceptable safety profile in both healthy volunteers and participants with PH1, PH2, and PH3. No significant safety findings have emerged from completed or ongoing studies.

Please see the Nedosiran IB for additional details of these clinical studies.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Risks associated with nedosiran may be characterized into 2 broad categories: risks associated with the siRNA molecule and risks associated with an off-target knockdown of *LDHA*.

2.3.1.1. Risks Related to the siRNA Molecule

To date, nedosiran sodium has been associated with little to no systemic toxicity in the nonclinical studies. Results of nonclinical toxicity studies of nedosiran sodium conducted to date are presented in Section 2.2.2.

Clinical observations associated with other siRNAs have included occasional reports of stimulation of pattern recognition receptors (e.g., Toll-like receptors) leading to cytokine release, inflammation, and ISRs, and low elevations of LFT. Clinical experience with the Dicerna GalXC platform suggests an enhanced safety profile with little to no evidence of systemic immune stimulation or toxicities in more than 200 patients and healthy volunteers. Mild, self-limiting ISRs have been reported.

2.3.1.2. Risks Related to LDHA Knockdown and Potential Off-target Effects

LDHA deficiency (Glycogen storage disease XI) is a very rare, near complete loss of LDHA function caused by mutations in the *LDHA* gene. People with this condition may experience exercise intolerance, characterized by fatigue, muscle pain, and cramps during exercise (Kanno et al., 1980; Nishimura et al., 1983). Liver-associated changes have not been reported.

Nedosiran sodium contains 4 GalNAc sugar residues that preferentially direct delivery of the siRNA to hepatocytes, due to their high expression of ASGPR. As such, adverse effects outside of the liver are unlikely at clinical doses. No changes in muscle performance were noted when *Ldha*-knockdown mice were subjected to exercise in a treadmill endurance test (Lai et al, 2018), and no adverse skeletal muscle effects were observed in monkeys at nedosiran sodium dose levels up to 300 times the minimally active dose. Nonetheless, in addition to measurement of plasma CK, participants should be monitored for signs and symptoms of muscle weakness or pain.

Nedosiran sodium shows high sequence specificity. In silico analysis suggests that it has minimal potential for off-target effects via siRNA hybridization to the human genome.

2.3.2. Pediatric Burden Assessment

With respect to the overall burden of the study, patients with PH have regular visits at their treating physician, which includes routine measurements of hematology and chemistry, vital signs, kidney ultrasound, ECG, echocardiography, and analysis of spot urine (Cochat et al., 2012). Therefore, the burdens of the current protocol procedures are considered minimal in comparison to the standard treatment for PH (see Table 2 for details). At-home visits have been incorporated into the study design to minimize burden of study participation.

At each study visit, pediatric participants and their parent(s) or guardian(s) will be asked a few study-specific questions to ensure that the burden of continued study participation is not too extensive. This pediatric burden assessment is in line with the requirements put forth in the European Commission's *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors* (18 September 2017).

Table 2: Risk/Burden Assessment

Procedure	Risk/Burden	Mitigation
Blood sampling, including cannulation	Risks include acute pain, bleeding, vessel injury, and, in rare instances, arterial vessel blockage, potentially leading to infection.	The risk/burden is minimal and not over and above the risk/burden associated with blood sampling as part of the standard treatment for PH.
12-lead ECG	Electrocardiography does not involve any invasive procedures.	Conducted in supine position after 10 minutes at rest. No risks identified.
Blood pressure measurement	Measurement of blood pressure may result in mild discomfort.	Measurements performed at a single time point with an appropriately sized blood pressure cuff. No risks identified.
Subcutaneous injection	The study drug is administered via SC injection. Subcutaneous injection is associated with pain, and may cause vasovagal reactions, allergic reactions, infections, and bleeding.	The risk/burden associated with SC administration of the study drug is minimal. This injection is outside the standard treatment for PH and therefore is assessed as a minimal risk/burden to participants. The investigator is obligated to anticipate and address injection site pain (for example, using a topical anesthetic).
Kidney ultrasound	Kidney ultrasound does not involve any invasive procedures.	Kidney ultrasound is part of the standard treatment for patients with PH. No risks identified.
Echocardiogram	Echocardiography does not involve any invasive procedures.	Echocardiography is part of the standard treatment for patients with PH. No risks identified. The echocardiogram should not be performed if it requires sedation.
Spot urine collection	Due to the frequency of collection in the current protocol, minor burden is involved.	Spot urine collection is part of the standard treatment for PH patients. Urine collection in this study does not involve catheterization or invasive procedures of any kind (unless this is already part of the participants standard of care). No risks identified.

2.3.3. Benefit Assessment

The biological relationship between urinary oxalate supersaturation and the subsequent calcifications in kidney and extra-renal organs has been well established (Hoppe et al., 2009; Hoppe, 2012; Cochat & Rumsby, 2013). The degree of hyperoxaluria has been shown to predict the development and severity of nephrocalcinosis and is described as a risk factor for ESRD in patients with PH (Zhao et al., 2016).

As increased urinary oxalate is an independent risk factor for the development of calcium oxalate crystallization, a reduction in oxalate excretion should lower the risk of calcium-oxalate supersaturation and the subsequent negative consequences on the renal system and beyond. Several researchers have demonstrated that pre-emptive liver transplantation normalizes oxalate

excretion and stabilizes or improves kidney function in long-term follow-up if no systemic oxalosis is present (Kemper et al., 1998; Galanti & Contreras, 2010; Perera et al., 2011).

Results from nonclinical studies of nedosiran demonstrated that a reduction of hepatic *Ldha* mRNA lowered or eliminated excess oxalate production in the livers of PH model mice and protected the kidney from calcium oxalate crystal deposition and the resultant damage. Based on results achieved in the murine models of PH, administration of nedosiran to participants with PH, who do not have systemic oxalosis, is expected to result in a measurable reduction in urinary oxalate.

Results from the completed Study DCR-PHXC-101 are summarized in Section 2.2.3.1 and demonstrate that single-dose administration of nedosiran can reduce the urinary oxalate burden in participants with PH1 and PH2 and potentially decrease the risk for the development of calcium oxalate crystallization.

2.3.4. Risk Management

Measures to minimize the risks to participants have been incorporated into the following study design elements:

- An SRC will review all safety and efficacy data after the first 2 participants aged 2 to 5 years old have completed Day 60 and every 3 months thereafter. Ad hoc meetings may also occur if needed as specified in the SRC charter.
- Clinical Laboratory Monitoring: At time of study entry, study participants are required to have safety laboratory values within acceptable ranges. Serial measurements of safety laboratory parameters (CBC, platelet count, creatinine, cytokines, complement, LFTs) and coagulation parameters are planned, with regular medical review by the medical monitor, as outlined in the medical management plan.
- Monitoring of signs and symptoms of muscle pain and/or weakness, along with measurement of plasma creatine kinase.
- The maximum blood volume to be collected from pediatric participants over the course of the study will be based on weight and will not exceed those specified in Table 5. Consult the Laboratory Manual for the blood draw priority list based on participant weight.
- If met with blood draw difficulty, the Investigator team will make not more than 3 attempts at venipuncture in the same day.

With regard to pediatric participants, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: *Clinical Investigation of Medicinal Products in the Pediatric Population* (E11, 20 July 2000) and the European Commission *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors* (18 September 2017) have been considered during the design of the trial, and blood volume minimized where possible. Practical considerations include the use of laboratories experienced in handling small volumes of blood for PK, PD, and laboratory safety analyses.

Wherever possible, routine clinical safety, efficacy, and PK blood samples will be collected at the same time point. Furthermore, indwelling catheters will be used where deemed appropriate by the Investigator team to minimize the potential distress of venipuncture.

2.3.5. Overall Benefit:Risk Conclusion

At present, no therapies are approved by regulatory authorities for the treatment of patients with PH2 or PH3. Lumasiran, a treatment for PH1, is approved in a limited number of countries, including the European Union. A number of supportive therapies are also used in an attempt to mitigate some of the effects of the disease, but affected patients are at considerable risk of serious complications like renal stones, nephrocalcinosis, renal failure, and systemic tissue damage due to oxalate deposition. Combined liver-and-kidney transplantation is the only causative therapy but is associated with short- and long-term complications as well.

Thus far nedosiran treatment has shown potential benefit to reduce or prevent the excess oxalate production in the liver. If sustained, this could eliminate the need for a liver transplantation.

The potential risks with nedosiran include low elevations of liver function tests, muscle damage, and stimulation of pattern recognition receptors (e.g., Toll-like receptors) leading to cytokine release, inflammation, and ISRs. These risks can be monitored and should be reversible after drug discontinuation. The results from the completed study, DCR-PHXC-101, demonstrate the potential for nedosiran to bring patients into a near-normal or normal range of their 24-hour Uox values. Continuous risk-benefit assessments will be conducted by the Sponsor, the Medical Monitor of the CRO, and the SRC on an ongoing basis.

3. 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 intact renal function based upon eGFR and serum creatinine	• Change from Baseline in the Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0, Clinical Practice Version (WPAI:PH, V2.0, CPV) – Caregiver in PH1, PH2, or PH3 participant subgroups

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multi-dose (3.5 mg/kg, not to exceed 170 mg), open-label, single-arm uncontrolled multicenter 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.

Following the up-to-35-day screening period, participants will return to the clinic for interim visits through Day 180 (6 months). At the discretion of the Investigator, visits on Days 2, 60, 120, and 150 may be conducted in the participant's home, through a combination of telemedicine and home nursing care (at-home telehealth visit). The total time on study for each participant is approximately 7 months. Participants completing this study may be eligible for enrollment into a long-term, open-label, extension study (see Section 6.7).

It is expected that approximately 25 participants will be screened such that approximately 20 participants will complete the study. Participants will receive monthly doses (3.5 mg/kg, not to exceed 170 mg) of nedosiran for 6 months.

Participants with PH3 will only be enrolled if Study DCR-PHXC-104 establishes proof of concept for nedosiran in lowering Uox in participants at least 6 years of age with PH3.

Modeling and simulation (M&S) was performed to determine the dose and dosing frequency for the birth to 5 years of age group in this study based on all available data for participants aged ≥ 6 years.

It is expected that the entire trial will have a 24-month duration.

4.2. Scientific Rationale for Study Design

This Phase 2, multi-dose, open-label, single-arm uncontrolled trial is the optimal design for evaluation of efficacy and safety of an investigational drug in the pediatric participants (birth to 11 years of age). The 6-month duration of the treatment period is considered sufficient to demonstrate a sustained effect of nedosiran in lowering Uox in participants with PH.

The primary endpoint of this Phase 2 study will be the percent and absolute change from Baseline to Month 6 in spot urinary oxalate-to-creatinine ratio. The degree of hyperoxaluria predicts the development and severity of nephrocalcinosis and is a risk factor for ESRD in participants with PH (Zhao et al., 2016). The average of 6 baseline spot urine oxalate-to-creatinine ratios at Screening will be above 2 times the 95th percentile for age to qualify for enrollment (Matos et al., 1999).

4.3. Justification for Dose

4.3.1. PK/PD Model for Dose Selection in Pediatric Participants (Birth to 11 Years)

The dose selection for the 6- to 11-year-old participants was based on safety, tolerability and PK-PD relationship between nedosiran and Uox excretion. The dose for 6- to 11-year-old participants was aided by PK and PK-PD simulations from adults and adolescents in previous studies of nedosiran. The dose was selected such that the 6- to 11-year-old participants will have

a similar exposure to nedosiran as participants receiving the 170 mg dose and to provide for a comparable proportion of participants with normal or near-normal levels of 24-hour Uox. Based on these simulations, a dose regimen of 3.5 mg/kg once monthly was selected. The dose has been shown to be safe and tolerable (following multiple Q1M dosing in this age category) in other clinical studies with nedosiran.

The dose selection for 0- to 5-year-old participants was based on safety, efficacy, PK, and PD considerations. Multiple doses of nedosiran (3.5 mg/kg once monthly) have been demonstrated to be safe and well tolerated in pediatric participants with PH in the 6- to 11-year age group (Study DCR-PHXC-201). No SAEs have been reported in the 6- to 11-year-old participants with PH.

Selection of dose was aided by PK-PD modeling simulation of data from participants aged 6 years and older. Based on these simulations, a dosing regimen of 3.5 mg/kg, not to exceed 170 mg, once monthly was selected for children aged 0 to 5 years.

The selected dosing regimen (3.5 mg/kg once monthly) for the 0 to 5-year age group is predicted to provide similar plasma and liver exposure ($AUC_{0\text{-}tau}$) of nedosiran as compared to the 6- to 11-year age group and a similar lowering of urinary oxalate.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Birth to 11 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Documented diagnosis of PH1, PH2, or PH3 confirmed by genotyping (historically available genotype information is acceptable for study eligibility).

3. Average spot Uox to creatinine ratio at Screening above 2 times the 95th percentile for age (Matos et al, 1999):

- > 0.44 mol/mol in participants < 6 months
- > 0.34 mol/mol in participants from 6 months to < 12 months
- > 0.26 mol/mol in participants 12 months to < 2 years
- > 0.20 mol/mol in participants from 2 to < 3 years and
- > 0.16 mol/mol in participants from 3 to < 5 years
- > 0.14 mol/mol in participants from 5 to < 7 years
- > 0.12 mol/mol in participants from 7 to 11 years

4. Estimated GFR at Screening ≥ 30 mL/min normalized to 1.73 m^2 BSA. See Section 8.2.6.1 for equations. For infants aged less than 12 months, serum creatinine below the 97.5th percentile of a healthy population (Boer et al., 2010).

5. Participants must have been on a stable treatment regimen for PH for 3 months prior to Day 1 and parent(s)/legal guardian should be willing to ensure participant remains on the same stable treatment regimen during the study. Dose adjustments for interval weight gain are acceptable.

Sex

6. Male or female

Male participants:

A male participant with a female partner of childbearing potential must agree to use contraception, as detailed in Section 10.5.2, during the treatment period and

for at least 12 weeks after the last dose of study intervention and refrain from donating sperm during this period.

Female participants:

A female participant is eligible to participate if she is not pregnant (see Section 10.5.1), not breastfeeding, and at least 1 of the following conditions applies:

Not a woman of childbearing potential (WOCBP) as defined in Section 10.5.1

OR

A WOCBP who agrees to follow the contraceptive guidance in Section 10.5.2 during the treatment period and for at least 12 weeks after the last dose of study intervention.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Note: If the childbearing potential changes after start of the study (e.g., a premenarchal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the Investigator, who should determine if a female participant must begin a highly effective method of contraception or a male participant must use a condom. If reproductive status is questionable, additional evaluation should be considered.

Informed Consent and Assent

7. Participant's parent or legal guardian is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

   a. For children younger than 12 years of age, assent will be based on local regulation. If assent is required, participant must be able to provide written assent for participation.

Other

8. A legal guardian or primary caregiver must be available to help the study-site personnel ensure follow up; accompany the participant to the study site on each assessment day according to the SoA (e.g., able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed.

9. Affiliated with or is a beneficiary of a health insurance system (if applicable per national regulations)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Prior renal or hepatic transplantation; or planned transplantation within the study period

2. Currently receiving dialysis or anticipating requirement for dialysis during the study period

3. Plasma oxalate (Pox) > 30 µmol/L at Screening

4. Documented evidence of clinical manifestations of severe systemic oxalosis (including preexisting retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations)

5. Presence of any condition or comorbidities that would interfere with study compliance or data interpretation or potentially impact participant's safety including, but not restricted to:

   a. Severe intercurrent illness
   b. Known causes of active liver disease/injury or transaminase elevation (e.g., alcoholic liver disease, nonalcoholic fatty liver disease/steatohepatitis [NAFLD/NASH])
   c. History of serious mental illness that includes, but is not limited to, schizophrenia, bipolar disorder, or severe depression requiring hospitalization or pharmacological intervention
   d. Clinically relevant history or presence of cardiovascular, respiratory, gastrointestinal, hematological, lymphatic, neurological, musculoskeletal, genitourinary, immunological diseases, including dermatological including rash, severe eczema or dermatitis, or connective tissue diseases or disorders

Prior/Concomitant Therapy

6. Use of an RNAi drug within the last 6 months

7. History of 1 or more of the following reactions to an oligonucleotide-based therapy:

   a. Severe thrombocytopenia (platelet count ≤ 100,000/µL)
   b. Hepatotoxicity, defined as ALT or AST > 3 times the upper ULN and total bilirubin > 2 × ULN or INR > 1.5
   c. Severe flu-like symptoms leading to discontinuation of therapy
   d. Localized skin reaction from the injection (graded severe) leading to discontinuation of therapy
   e. Coagulopathy/clinically significant prolongation of clotting time

Prior/Concurrent Clinical Study Experience

8. Participation in any clinical study in which they received an IMP within 4 months or 5 times the half-life of the drug (whichever is longer) before Screening

   a. For IMPs with the potential to reduce urine and/or plasma oxalate concentrations, these concentrations must have returned to historical baseline levels prior to Screening

Diagnostic assessments

9. Liver function test (LFT) abnormalities: ALT and/or AST > 1.5 × ULN for age and gender

Other Exclusions

10. Known hypersensitivity to nedosiran, or any of its ingredients

11. Inability or unwillingness to comply with the specified study procedures, including the lifestyle considerations detailed in Section 5.3.

5.3. Lifestyle Considerations

During this study, the parent(s)/legal guardian are asked to ensure the participant:

- Refrain taking vitamin C supplements, including multivitamins, for 24 hours prior to and during the timeframe when spot urine specimens are collected
- Continue to follow standard of care for PH, including, but not limited to hyperhydration regimens, oral potassium citrate administration, and treatment with vitamin B6 (if applicable)

5.3.1. Meals and Dietary Restrictions

During this study, the parent(s)/legal guardian are asked to ensure the participant:

- Avoids oxalate-rich foods

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Rescreened participants will be assigned a new participant number for re-screening. Potential participants may undergo rescreening only with approval of the Sponsor.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Nedosiran (also known as DCR-PHXC) is a synthetic RNAi drug that consists of a double-stranded oligonucleotide conjugated to GalNAc ligands. Nedosiran is a sterile formulation of drug substance (nedosiran sodium) in WFI, intended for SC administration.

Nedosiran is not commercially available in any country.

The total dose will be based upon body weight recorded on study Day 1, and for participants ≥ 6 months of age at Screening, the dose will remain constant throughout the study (i.e., the dose administered on Day 1 will be the dose administered at all following visits regardless of any change in body weight). For participants < 6 months of age at Screening, the dose will be adjusted at Day 90 to capture changes in weight; no other dose adjustments are allowed.

ARM Name	**Active**
Intervention Name	Nedosiran
Type	Drug
Dose Formulation	Sterile formulation of drug substance (nedosiran sodium) in WFI
Unit Dose Strength(s)	170 mg/mL (sodium salt; 160 mg/mL free acid)
Dosage Level(s) (calculated from sodium salt)	Multi dose 3.5 mg/kg, not to exceed 170 mg
Route of Administration	SC injection (thigh or abdomen)
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor or designee
Packaging and Labeling	Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement.
Alias	DCR-PHXC

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Handling and Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply study intervention. Only authorized site staff, visiting nurses, or the participants' parents/caregivers may administer study intervention.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.2.2. Storage

Nedosiran is to be stored at 2°C to 8°C (inclusive). Nedosiran is to be stored in an appropriately secured location in a refrigerator, and storage must comply with institutional procedures in effect at the study site for handling investigational products. Access must be limited to authorized clinic personnel. A temperature log will be maintained.

At home, the participant's parent or caregiver will store nedosiran in a refrigerator (2°C to 8°C). The product should not be allowed to freeze or be placed next to the freezer compartment or a freezer pack.

6.2.3. Preparation and Administration

Study intervention will be prepared by the pharmacist or designee.

A second medically qualified person must check the dose preparation prior to administration to be sure the correct dose has been prepared.

The product should be allowed to warm to room temperature for approximately 1 hour but no more than 4 hours before administration.

Nedosiran is administered as a SC injection into the thigh or abdomen using a 25- to 27-gauge needle, 3/8 to 5/8 inches long. The maximum injection volume in participants is 0.5 mL; if the participant's weight requires an injection volume > 0.5 mL, the total dose will be administered as 2 SC injections of equal volume.

As allowed by local health authorities and ethics committees, after the first 2 injections of nedosiran, study intervention may be administered at home at the Investigator's discretion for those months at which a study-site visit is not required. For participants 0 to 5 years old, visiting nurses may administer SC injections at home. For participants 6 to 11 years old, the participants' caregivers or visiting nurses may administer SC injections at home. For any participant whose caregiver administers study drug during at home visits, the participants' caregivers will

administer nedosiran in the presence of the Investigator/study staff to confirm proper technique at clinic visits. A portfolio of training materials will be provided for at-home reference.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable eCRF, if required.

6.4. Study Intervention Compliance

Study intervention will be administered by a member of the study staff or a caregiver/visiting nurse for at-home visits. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

With respect to at-home dosing, participants' caregivers will complete a dosing diary and will return all empty and/or unused vials to the study site at each visit.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants taking pyridoxine (vitamin B6) must have been at a stable dose for at least 3 months (or as applicable for those less than 3 months of age) prior to Day 1 and must remain on the same stable dose throughout the study. Dose adjustments for interval weight gain are acceptable.

Participants should avoid taking vitamin C supplements, including multivitamins, for 24 hours prior to and during the timeframe when spot urine samples are collected. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor (if required).

6.5.1. Prohibited During the Study

Participation in any other clinical study involving an IMP is prohibited during this study.

6.5.2. Rescue Medicine

Not applicable.

6.5.3. COVID-19 and Other Vaccine Administration

To allow discernment of AEs related to the administration of vaccines from those related to administration of study intervention, vaccines should not be administered in the 7 days prior to or following scheduled administration of study intervention.

6.6. Dose Modification

No dose modifications are allowed, except for dose adjustments based upon weight at Day 90 for participants < 6 months of age at Screening.

6.7. Intervention After the End of the Study

Participants successfully completing study DCR-PHXC-203 may be screened for entry into the roll-over study (DCR-PHXC-301) at the Day 180, EOS visit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1.1. Discontinuation of Study Intervention Stopping Rules for Individual Participants

Study intervention for an individual participant may be permanently discontinued at any time at the discretion of the Investigator.

Study intervention for an individual participant will be permanently discontinued for any of the following:

- any SAE possibly, probably, or definitely related to study intervention; unless, before the next scheduled dose, the SAE is reconsidered to be not related to study intervention or has resolved AND continued drug treatment in the study is considered safe by the SRC.
- any of the changes in hepatic function detailed in Section 7.1.1.1.
- pregnancy, as detailed in Section 10.5.

Discontinuation from study intervention does not mean discontinuation from the study. Remaining visits and study procedures should be completed as indicated by the SoA.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1.1. Drug-Induced Liver Injury Monitoring

See Section 10.5.

7.1.1.2. Temporary Discontinuation

Temporary discontinuation of study intervention may be allowed due to changes in hepatic function, see Section 10.5.

7.1.1.3. Rechallenge

Rechallenge with study intervention may be allowed following changes in hepatic function, see Section 10.5.

7.1.2. Study Stopping Rules

In the event of a life-threatening or fatal SAE that is determined to be at least possibly related to study drug, the study will be suspended (i.e., further enrollment and dosing in the study will be interrupted) and an ad hoc SRC meeting will happen. Continuation of the study would require approval by the regulatory authorities. The Sponsor will notify all sites promptly if the study is suspended or terminated. In the event that the study is suspended or terminated, all ongoing participants will continue to be followed for safety assessments as indicated in the SoA (Section 1.3).

7.2. Participant Discontinuation/Withdrawal from the Study

The participant's parent or legal guardian has the right to withdraw permission (consent) at any time during the study or the participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant's parent or legal guardian withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant or participant's parent or legal guardian may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Participants who sign the ICF but do not receive the study intervention may be replaced. Participants who sign the ICF and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may be replaced at the discretion of the Sponsor.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant's parent or legal guardian and reschedule the missed visit as soon as possible and counsel the participant's parent or legal guardian on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant's parent or legal guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.8).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA presented in Table 1. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Spot Urine Collection

Oxalate is a dicarboxylic acid that is a normal end-product of metabolism. Most oxalate in the body is produced in the liver. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. In individuals with PH, mutations in the *AGXT*, *GRHPR*, or *HOGA1* gene result in the overproduction of oxalate by the liver, which causes increased oxalate excretion by the kidneys.

The primary measurement of oxalate in the urine will be via spot urine collection. The second morning void is thought to offer the least variability in terms of Uox/ creatinine.

Urine samples will be collected for the determination of Uox and creatinine. Six spot urine samples (3 of which must be second morning void) will be collected over a 3-day period during Screening. Baseline is defined as the average of the 6 screening values.

Four on-treatment spot urine samples (2 of which must be second morning void) will be collected over a 2-day period on a monthly basis.

Participants should avoid consuming vitamin C, including multivitamins, in the 24 hours preceding urine collection.

Any participant who prematurely discontinues study intervention should perform 4 spot urine collections as directed by the Medical Monitor.

Complete instructions for the spot urine collection, including in infants, will be provided in the Urine Collections Instructions.

8.1.2. Plasma Oxalate (Pox)

Plasma oxalate concentration is a reflection of the body pool size. The Pox pool size is increased in individuals with PH and impaired renal function. When the pool increases, oxalate may precipitate in tissues and cause toxicity.

Complete instructions for collection and handling of samples will be provided in the Central Laboratory Manual.

8.1.3. Kidney Assessments

Participants with PH are predisposed to the development of multiple and recurrent urinary tract (urolithiasis) and kidney (nephrolithiasis) stones. This deposition of calcium oxalate in the renal parenchyma produces tubular toxicity and renal damage that is compounded by the effects of renal calculi-related obstruction and frequent superimposed infections (Cochat & Rumsby, 2013).

8.1.3.1. Kidney Stone Events and Stone Burden

Parents or legal guardians of participants will provide a 12-month history of stone events (or as applicable for those less than 12 months of age) experienced by the participant at Screening and will report any stone events during the study.

For the purpose of this study, “stone events” are all events that meet one or more of the following criteria:

- **Renal stone requiring medical intervention** (e.g., outpatient procedures such as lithotripsy, or hospitalization and/or inpatient surgical intervention for confirmed stone related pain and/or complications)
- **Stone passage with or without hematuria**
- **Renal colic requiring medication**

Concurrent events will be defined as events occurring within the same 4-week (28-day) window.

Note: Although a change from baseline in the rate of stone events is an efficacy endpoint, stone events will be considered AESIs (Section 10.4.3).

For the purpose of the study, “stone burden” is a term used primarily as a metric for quantifying and qualifying changes from baseline in the overall number and 2-dimensional surface area of renal stones, as observed via kidney ultrasound over the course of the study.

Taken together, the terms stone event and stone burden will be used to derive meaningful quantification and qualification of overall impact of clinical sequelae of renal stones during the course of the trial.

8.1.3.2. Kidney Ultrasound

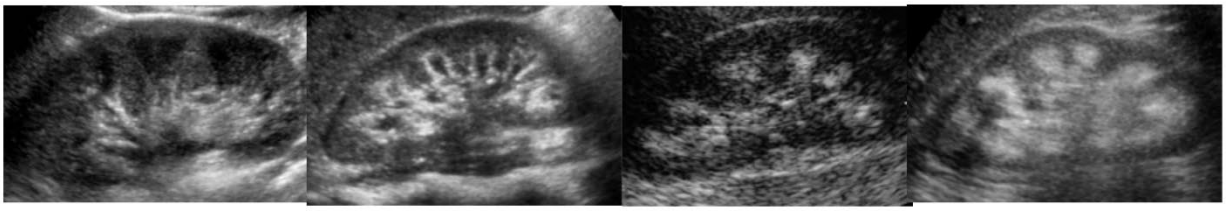
Kidney ultrasound will be performed at time points specified in the SoA. The kidneys should be examined in the longitudinal (sagittal) and transverse scan planes, ideally with images acquired in both the supine and prone positions. A linear array transducer with higher center frequencies should be used in participants younger than 18 years of age. Participants should have a full bladder during image acquisition.

All kidney ultrasound data will be transmitted to a standalone imaging vendor, where qualified personnel will perform central overread of all images. The number and size of stones will be determined by the central readers. The details of any findings should be placed in the participant's source record and recorded in the eCRF. The end-to-end process of centralized kidney ultrasound overread is detailed in a separate DCR-PHXC-203 Imaging Review Charter (Cardiabase).

Centralized overread will include standardized nephrocalcinosis grading in accordance with the staging criteria outlined in Figure 1.

Figure 1: Standardized Nephrocalcinosis Grading

- Grade 0: No echogenicity
- Grade 1: Mild echogenicity around medullary pyramid borders
- Grade 2: Moderate echogenicity around and inside pyramids
- Grade 3: Severe echogenicity of entire pyramids



From Boyce et al., 2013

8.1.4. Quality of Life Assessments

Health-related quality of life (HRQOL) surveys will be administered to pediatric participants or their parents or legal guardians at Screening and EOS as indicated in the SoA. For consistency, the same member of the study staff should administer the surveys to a participant at both Screening and EOS. When possible, HRQOL surveys should be completed prior to other study-specific assessments and procedures.

8.1.4.1. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL™) is a modular approach to measuring HRQOL in healthy pediatric participants 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 WHO in 1948 (physical, emotional, and social functioning), as well as role (school) functioning (Varni et al., 1998; Varni et al., 2001).

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. Items are reverse-scored on a 0 to 4 Likert scale and linearly transformed to a 0 to 100 scale, so that higher scores indicate better functioning and HRQOL. Scale Scores are the sum of the items in each dimension, divided by the number of items answered.

Age-appropriate self-reporting questionnaires are available for children aged 5 to 7 years and 8 to 11 years. Children (8-11) may self-administer the PedsQL after introductory instructions from the administrator. If the administrator determines that a child is unable to self-administer the PedsQL (e.g., due to illness, fatigue, or reading difficulties), the PedsQL should be read aloud to the child. For children aged 5 to 7 years, the PedsQL should be administered by reading the instructions and each item to the young child word for word. Parental proxy reports are available for children aged 1 to 12 months, 13 to 24 months, 2 to 4 years, 5 to 7 years, and 8 to 11 years. Parents may self-administer the PedsQL after introductory instructions from the administrator.

If a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent/guardian.

As children age, the *same* questionnaire administered at baseline should continue to be used throughout the study, even if the child "ages out" of the baseline questionnaire.

In addition to the PedsQL Generic Core Scales, parents of pediatric participants will complete the PedsQL Family Impact Module (Varni et al., 2004). The PedsQL Family Impact Module was designed to measure the impact of pediatric chronic health conditions on parents and the family. The 36-item Module measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The Module also measures parent-reported family daily activities and family relationships.

8.1.5. Reporting Fluid Intake

Hyperhydration regimens are a central feature in the conservative management of urinary oxalate levels in patients with PH. As such, the participant's parent or legal guardian are asked to ensure the participant maintains a consistent fluid intake throughout the study (Section 5.3). For non-breastfed participants, the participant's parent or legal guardian will be asked to report the participant's average daily fluid intake during the 4- to 7-day period before each of the spot urine collection periods, including the collections conducted during Screening. It is preferred that intake for each of the 7 days be recorded, however, should logistic difficulties require a shorter recording period, intake over at least the 4 days prior to the collection will be recorded.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Weight, Height, Length and Body Surface Area

Body weight and height should be measured without shoes.

Length, measured in the recumbent position, is the correct linear measurement for participants younger than 24 months of age or children aged 24 to 36 months who cannot stand unassisted. Length will be measured via a calibrated length board.

Body weight will be recorded in kg. Weight should be measured on the same calibrated scale at each scheduled visit.

Height will be recorded in cm and should be measured on the same calibrated stadiometer at each scheduled visit.

Body surface area will be calculated using the following formula (DuBois & DuBois, 1916):

BSA = (Weight$^{0.425}$ × Height$^{0.725}$) × 0.007184; with weight in kilograms and height in centimeters.

8.2.2. Physical Examinations

A full physical examination will include a complete review of body systems: eyes, ears, nose, and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, and neurological. A full physical exam will be conducted at Screening and EOS/early termination (ET).

A brief physical examination will include, at a minimum, chest/respiratory, heart/cardiovascular, dermatological/skin, and gastrointestinal/liver. The physical examination performed at other scheduled visits (Day 1 through Day 150) or unscheduled visits may be a brief or full physical examination at the Investigator's discretion. For at-home visits, the home-health nurse will provide in-person support to the Investigator in assessing the participant.

Study intervention injection sites should be inspected at each visit.

8.2.3. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. An age-appropriate cuff size should be used for blood pressure measurements.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Temperature will be obtained in degrees Celsius (°C) via the same method throughout the study, pulse rate will be counted for a full minute and recorded in beats per minute, and respirations will be counted for a full minute and recorded in breaths per minute. Note that when a 12-lead ECG is performed at the same time as vital signs, heart rate should be taken from the ECG.

If multiple assessments are due at the same time point, PK sampling should be performed at the nominal time point, with the preferred order of assessments ECG, vital signs, PK, and then other assessments.

8.2.4. Electrocardiograms

Standard 12-lead ECGs will be performed with the participant in the supine position, after the participant has rested comfortably for 10 minutes. The parameters assessed will be rhythm, ventricular rate, PR interval, QRS duration, QT interval, and corrected QT interval (QTcF, Fridericia correction). The Investigator or designee is responsible for reviewing the ECG(s) to assess whether the results are within normal limits and to determine the clinical significance of the results. These assessments will be recorded on the eCRF.

Standardized ECG acquisition equipment will be provided to all clinical trial sites at the start of the trial, to ensure parity across all sites. All ECG data will be transmitted to a stand-alone imaging vendor, where qualified personnel will perform central overread of all ECG readouts. The end-to-end process of centralized ECG acquisition and overread is detailed in a separate

DCR-PHXC-203 Imaging Review Charter (Cardiabase). Site personnel will be trained in the processes relating to ECG acquisition and transmission. Sites that have completed training for a similar Dicerna-sponsored study within the past 2 years are not required to repeat ECG training.

If multiple assessments are due at the same time point, PK sampling should be performed at the nominal time point, with the preferred order of assessments ECG, vital signs, PK, and then other assessments.

8.2.5. Echocardiogram with Doppler

Echocardiography will be performed by a qualified pediatric sonographer/physician (and overread by a pediatric cardiologist) using a standard, commercially available ultrasound machine. The echocardiography technician should perform standard 2-D transthoracic echocardiography with Doppler as described by the ASE recommendations (Picard et al., 2011). The full ASE protocol need not be followed but should include a gross assessment of the overall cardiac anatomy and quantitative evaluation of basic ventricular systolic function. The final echocardiogram report should note the details of the protocol that were followed. The overreading cardiologist should note any findings in the department's standard reporting format. Findings from the echocardiogram should be included in the participant's source record and documented in the eCRF. Any findings that, in the opinion of the Investigator, may disqualify the participant should be discussed with the Medical Monitor. NOTE: If for an individual participant the echocardiogram cannot be performed without sedation (e.g., due to age), the echocardiogram should not be performed. The omission of an echocardiogram due to sedation requirement should not be considered a protocol deviation.

Additionally, all echocardiogram data will be transmitted to a stand-alone imaging vendor, where qualified personnel will perform postprocessing of echocardiogram data and central overread of all images. The end-to-end process of centralized echocardiogram overread and postprocessing is detailed in a separate DCR-PHXC-203 Imaging Review Charter (Cardiabase).

8.2.6. Clinical Safety Laboratory Assessments

See Table 4 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency. See Section 10.3 for directives regarding prioritization of blood draws.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Table 4, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.6.1. Estimated Glomerular Filtration Rate (eGFR)

The eGFR (mL/min/1.73 m^2) will be calculated using the multivariate Schwartz equation in participants aged 12 months and older (Figure 2).

In Japan, eGFR (mL/min/1.73 m^2) will be calculated using the Uemura creatinine-based equation in participants aged 2 years and older (Figure 3) or the Uemura cystatin C-based equation in participants aged 12 months to < 2 years (Figure 4).

Estimating GFR in infants is challenging because GFR measured using exogenous markers is burdensome and is not routinely performed in this population. As participants enrolled as infants younger than 12 months of age will not have a baseline eGFR recorded, no calculation of eGFR will be required as these participants age up throughout the study. In these participants younger than 12 months of age, serum creatinine will be monitored for renal health (see Section 8.2.6).

Figure 2: Multivariate Schwartz eGFR Equation

$$eGFR = 39.8 \times [ht/Scr]^{0.456}[1.8/cysC]^{0.418}[30/BUN]^{0.079}1.076^{male}[ht/1.4]^{0.179}$$

where
ht (height) = meters
Scr (serum creatinine) = mg/dL
cysC (cystatin C) = mg/L
BUN (blood urea nitrogen) = mg/dL

From Schwartz et al., 2012

Figure 3: Uemura Creatinine-based eGFR Equation (Japanese Participants ≥ 2 Years of Age)

eGFR = 110.2 × (reference serum Cr/patient's serum Cr) + 2.93

where
Reference serum Cr levels (y) are shown by 2 equations of body length in m (x):

Males : $y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$

Females : $y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778$

From Uemura et al, 2014a

Figure 4: Uemura Cystatin C-based eGFR Equation (Japanese Participants 12 Months to < 2 Years of Age)

inulin GFR = 104.1 × 1/serum cysC − 7.80
where
cysC (cystatin C) = mg/L

From Uemura et al., 2014b

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, and AESI are located in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until 30 days after the last day of study participation.

All AEs will be collected from the signing of the ICF until the EOS/ET time point specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant or participant's parent or legal guardian is the preferred method to inquire about AE occurrences.

Study-site staff should instruct the participant's parent or legal guardian on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in neonates, infants, and toddlers.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 10.4.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours of learning of the event) by the Investigator to the SAE Submission Coordinator of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

For all studies, Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details will be collected of all pregnancies in female participants occurring after the start of study intervention and until 12 weeks after the last dose of study intervention.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

See Section 10.4.3.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than the protocol specified dose will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the CRO Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 28 days).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose continuation, dose interruptions, or modifications will be made by the Investigator in consultation with the CRO and Sponsor Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of nedosiran at the timepoints specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the Central Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Pharmacokinetic parameters to be determined may include AUC, C_{max}, C_{min}, t_{max}, and $t_{½}$, as calculable. Additional parameters may be reported if deemed appropriate. The population PK parameters may be reported separately from the CSR.

8.6. Pharmacodynamics

Pharmacodynamic parameters other than urinary oxalate and Pox (Section 8.1.1 and Section 8.1.2) are not evaluated in this study.

8.7. Genetics

Genetics will not be evaluated in this study. However, participants without documented PH genotyping must provide a DNA sample for testing at Screening.

8.8. Biomarkers

See Section 8.1.1 and Section 8.1.2 for descriptions of urinary and plasma oxalate assessments.

8.9. Immunogenicity Assessments

Antibodies to nedosiran will be evaluated in plasma samples collected from all participants according to the SoA. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

The detection and characterization of antibodies to nedosiran will be performed by or under the supervision of the Sponsor.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to nedosiran.

8.10. Medical Resource Utilization and Health Economics

In order to understand how a participant's use of health care services (e.g., number of physician visits, emergency room visits) and the parent or legal guardian's out-of-pocket expenses vary across time, and if their utilization changes with PH outcomes, there will be several questions on the eCRF around medical care for PH. The parent/guardian will respond regarding the treatment for their child. Parent/guardian will be asked to report the number of physician visits (by specialty: nephrologist, urologist, PCP, and ophthalmologist) and the number of ER, urgent care, and/or inpatient visits due to the participant's PH.

Two health economics queries will also be made. The first is to ask the participant's parent/guardian what was spent out of pocket for PH treatment (i.e., hyperhydration). The second question will ask how much work time was lost to care for their child. This is only for parents/guardians employed full time outside of the home; if the parent/guardian is a full-time student, they will be asked how much classroom time was lost due to their child's PH.

8.10.1. Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0, Clinical Practice Version (WPAI:PH, V2.0, CPV) – Caregiver

The WPAI:PH, V2.0, CPV (Reilly et al, 1993) measures work productivity of the caregiver, including missed time at work, because of a child's PH. The assessment includes 6 questions related to the effect of the participant's PH on caregiver's ability to work and perform regular activities.

The 6 items are as follows:

1. currently employed
2. hours missed due to specified problem (caregiving for PH child)
3. hours missed other reasons
4. hours actually worked
5. degree problem affected productivity while working
6. degree problem affected regular activities

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypothesis testing will be performed. Statistical analysis will be primarily descriptive.

9.2. 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 pediatric participants (birth to 11 years of age) with PH1, PH2 or PH3 and relatively intact renal function.

9.3. Populations for Analyses

For the purposes of analysis, the following populations are defined:

Population	Description
Modified Intent-To-Treat (MITT) Population	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	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.
Safety Population	All participants who received at least 1 dose of study intervention
Pharmacokinetic Population	The PK Population includes all participants who received at least 1 dose of study intervention (without major dosing violations) and have at least 1 evaluable postdose PK assessment

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section, including the procedures for accounting for missing, unused, and spurious data.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

Sensitivity analyses may be conducted and will be described in further detail in the SAP.

9.4.1. General Considerations

All statistical analyses will be descriptive in nature. No tests of statistical inference are planned.

9.4.2. Primary Endpoint

The primary endpoint in this study is change from Baseline to Month 6 in spot urinary oxalate-to-creatinine ratio by PH1, PH2, or PH3 participant subgroups. The percent and absolute change in average spot urinary oxalate-to-creatinine ratio from Baseline to Day 180 will be summarized by PH1, PH2, or PH3 participant subgroups.

9.4.3. Secondary Endpoints

9.4.3.1. Efficacy Endpoints

Secondary efficacy endpoints are listed below. Additional details will be provided in the SAP.

Endpoint	Statistical Analysis
Percentage of participants with spot urinary oxalate-to-creatinine ratio ≤ the ULN or ≤ 1.5 x ULN at any time point through Month 6	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 by PH1, PH2, or PH3 participant subgroups.
Change from Baseline in eGFR at Month 6	The percent change from baseline in eGFR at Month 6 (only in participants ≥ 12 Months of age at Screening) will be summarized by PH1, PH2, or PH3 participant subgroups.

9.4.3.2. Safety Endpoints

All safety analyses will be performed on the Safety Population. The incidence and nature of TEAEs and SAEs, along with change from Baseline in 12-lead ECG, physical examination findings, vital sign assessments, and clinical laboratory tests will be summarized.

Adverse events will be defined as treatment emergent if they have an onset or worsen in severity after a participant receives the study intervention. Treatment-emergent AEs will be summarized by SOC and preferred term according to the MedDRA. Treatment-emergent AEs will be further summarized by severity and relationship to study intervention. Adverse events leading to discontinuation, SAEs, and deaths will be summarized/listed.

Descriptive statistics will be provided for absolute values and changes from baseline in physical examination findings, vital sign measurements, ECGs, and clinical laboratory results at each timepoint.

9.4.3.3. Pharmacokinetic Endpoints

Pharmacokinetic analyses will be described in the SAP finalized before database lock. The population PK analysis will be presented separately from the main CSR.

9.4.4. Tertiary/Exploratory Endpoint(s)

Exploratory efficacy endpoints are listed below. Additional details will be provided in the SAP.

Endpoint	Statistical Analysis
Percent and absolute change in plasma oxalate over time	The percent and absolute change in plasma oxalate will be summarized by PH1, PH2, or PH3 participant subgroups.
Change from Baseline in annualized stone event rate	The change from Baseline in annualized stone event rate will be summarized by PH1, PH2, or PH3 participant subgroups.
Change from Baseline in the Pediatric Quality of Life Inventory (PedsQL™)	The change from Baseline in the PedsQL™ will be summarized by PH1, PH2, or PH3 participant subgroups.
Change from Baseline in the Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0, Clinical Practice Version (WPAI:PH, V2.0, CPV) – Caregiver	The change from Baseline in the WPAI:PH, V2.0, CPV – Caregiver will be summarized by PH1, PH2, or PH3 participant subgroups.

9.5. Interim Analyses

No formal interim analyses are planned, but the Sponsor reserves the right to conduct interim analyses if needed to support regulatory activities. Safety and efficacy data will be provided to the SRC on an as-needed basis.

9.6. Safety Review Committee (SRC)

The SRC will review safety and efficacy data on a periodic basis as described in the SRC charter. In addition, the SRC will closely monitor any changes in the PK (as appropriate), PD, or clinical efficacy, as well as any emerging events, such as anaphylaxis or hypersensitivity reactions that may suggest the development of ADAs.

The SRC will be comprised of an independent SRC chair (pediatric nephrologist), the Principal Investigator from each study site with a participant currently in the study (either having been dosed, or about to be dosed), or their designee, the Sponsor Medical Monitor, an independent ethicist, and the CRO Medical Monitor. Further operational details, including the timing of SRC meetings, will be pre-specified in the SRC charter.

On 13-Sept-2022, the SRC reviewed safety data from four 2- to 5-year-old participants with at least 60 days of exposure in this study. No related severe AEs or related SAEs were reported in these participants. Following the safety review, the SRC affirmed that the overall risk-benefit balance remained positive and approved the enrollment of participants younger than 2 years of age.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines (CIOMS VI, 2005)
- Applicable ICH GCP Guidelines
- Applicable laws and regulations, including privacy laws

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modifications to the protocol will require competent authority approval before implementation, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

Each interested prospective participant (or legally authorized representative) will receive an informed consent document that contains study information and be given ample time to read the information and consider participation. The Investigator or his/her representative will explain the nature of the study and its risks and potential benefits to the prospective participant or his/her legally authorized representative and answer all questions regarding the study. If the participant's treating physician is also the Investigator, he/she may not administer and witness the provision of informed consent. Administration of consent must be performed by another physician from the study team, to keep the roles of physician and researcher separated.

Prospective participants must be informed that the study involves research, their participation is voluntary, and that the choice not to participate or to discontinue the study at any time will involve no penalty or loss of benefits to which the individual is otherwise entitled. Consenting participants, or their legally authorized representative (parent or legal guardian for participants younger than 18 years or the local age of majority), will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. For children younger than 12 years of age, assent will be based on local regulations.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. As children and adolescents age, they must be re-consented to the appropriate ICF based on current age. Participants must be informed of any new information that arises during the course of the study which might be relevant to their willingness to continue in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant (or legally authorized representative) must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law, including the General Data Protection Regulation for all clinical studies conducted in the European Union. The level of disclosure must also be explained to the participant (or legally authorized representative) who will be required to give consent for their data to be used as described in the informed consent.

The participant (or legally authorized representative) must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

After completion and publication of the study, and de-identification, all individual data collected during the trial will be shared with investigators, whose proposed use of the data will have been approved by an independent review committee immediately following the publication of the entire study results.

Study results will be posted to the European Clinical Trials database (EudraCT) not later than 6 months after the database is locked. Study results will be posted at www.clinicaltrials.gov not later than 12 months after the database is locked.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request

previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

1. Investigator noncompliance with the protocol, GCP, or regulatory requirements
2. Unsatisfactory enrollment with respect to quantity or quality
3. Incomplete data collection; inaccurate or knowingly false data submission
4. The Principal Investigator is no longer capable of performing the tasks of the principal investigator, and no replacement can be found.
5. The SRC determines that termination of the study is in the best interest of the research participants
6. The Sponsor, Investigator or IRB/IEC determines that continuation of the study will not serve any scientific purpose
7. Circumstances beyond the control of the Sponsor or Investigator make it unreasonable to require the study's continuation
8. A request to discontinue the study by a regulatory or health authority

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

Table 3 summarizes the parameters that will be determined spot urine collections. Additional laboratory results may be reported on these samples. These additional tests would not require additional collection of urine.

Table 3: Parameters Determined from Urine

Laboratory Assessment	Parameters
Spot urine	urinary oxalate urinary creatinine urinary oxalate-to-creatinine ratio

The tests detailed in Table 4 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 4: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**	
Hematology	red blood cell count hemoglobin hematocrit mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) reticulocytes platelet count mean platelet volume (MPV)	White blood cell count: Lymphocytes, abs and % Monocytes, abs and % Eosinophils, abs and % Neutrophils, abs and % Basophils, abs and %
Clinical Chemistry	alanine transaminase (ALT) aspartate transaminase (AST) glutamate dehydrogenase (GLDH) gamma-glutamyl transferase (GGT) alkaline phosphatase (ALP) bilirubin (total and direct) lactate dehydrogenase (LDH) total protein albumin	creatine kinase (CK) sodium chloride potassium creatinine blood urea nitrogen (BUN) cystatin C (for calculation of eGFR)
Routine Urinalysis	specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick microscopic examination (if blood or protein is abnormal)	
Pregnancy testing	Serum or urine human chorionic gonadotropin (hCG) pregnancy test (WOCBP)	
Coagulation Parameters	International normalized ratio (INR) Prothrombin time (PT)	
Antibodies	Antidrug antibodies (samples will be tested when an assay is available)	
Other Tests	Plasma oxalate	

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Volume of Blood

The maximum blood volume to be collected from pediatric participants over the course of the study will be based on weight and will not exceed those specified in Table 5. Consult the Laboratory Manual for the blood draw priority list based on participant weight.

Table 5: Maximum Allowable Research-related Blood Sample Volumes

Body Weight (kg)	Circulating Total Blood Volume (mL)	Max. Allowable Sample Volume over 4 Weeks (mL) – 3% of Total Blood Volume	Max. Allowable Sample Volume at Single Time (mL) – 1% of Total Blood Volume
0.5 – 1.5	50 – 150	1.5 – 4.5	0.5 – 1.5
2.5 – 5	250 – 500	7.5 – 15	2.5 – 5
5 – 12	480 – 960	14.4 – 28.8	4.8 – 9.6
12 – 20	960 – 1600	28.8 – 48	9.6 – 16
20 – 30	1600 – 2400	48 – 72	16 – 24
30 – 70	2400 – 5600	48 – 168	24 – 56

Note: Total blood volume is approximately 80 to 90 mL/kg body weight, in neonates approximately 100 mL/kg body weight. Of note: when routine health care requires significant blood sampling, these maximums may even be excessive.
Source: European Commission's *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors* (18 September 2017)

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

10.4.1.1. Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose itself will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported, regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.4.1.2. Events Not Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

1. **Results in death**
2. **Is life-threatening**

   The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. **Requires inpatient hospitalization or prolongation of existing hospitalization**

   In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Pre-planned hospitalizations scheduled, prior to signing the ICF, for an elective medical/surgical procedure do not meet this criterion.

4. **Results in persistent disability/incapacity**

   The term disability means a substantial disruption of a person's ability to conduct normal life functions.

   This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. **Is a congenital anomaly/birth defect**
6. **Other situations**

   Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

   Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3. Definition of Adverse Event of Special Interest

An AESI is a noteworthy event for the particular product or class of products that a Sponsor may wish to monitor carefully (CIOMS VI, 2005).

10.4.3.1. Events Meeting the AESI Definition

Injection site reaction (ISR):

An ISR 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:

Signs or symptoms at the injection site (e.g., erythema, swelling) with a time to onset of 4 or more hours from the time of study intervention administration will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 criteria for ISR, detailed below. If any of the CTCAE criteria for ISR are met, the event will be recorded as an ISR and graded in accordance with Table 6.

Table 6: Grading of Injection Site Reactions, CTCAE v 5.0

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Individual signs or symptoms at the injection site with a time to onset of less than 4 hours from the time of study intervention administration will be recorded as AEs (not as an ISR) and graded in accordance with the intensity categories detailed in Section 10.4.4.2.

Muscle pain or weakness:

Because the nonclinical safety program in mice identified potential off-target effects on skeletal muscle, participants should be monitored for signs and symptoms of muscle weakness or pain, in addition to measurement of plasma CK.

Kidney Stone Events

Patients with PH are predisposed to the development of multiple and recurrent urinary tract and kidney stones. As participants may enter the study with pre-existing stones, stone events (as defined in Section 8.1.3.1), while being considered in the evaluation of efficacy, will be considered AESI.

10.4.4. Recording and Follow-Up of AE and/or SAE

10.4.4.1. AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF.

- It is not acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor or Medical Monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.4.4.2. Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

  An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE (see Section 10.4.2), NOT when it is rated as severe.

10.4.4.3. Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the SAE Submission Coordinator.

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions will be used in assessing causality:

- **Not Related**: Event for which sufficient evidence exists to conclude that the etiology is unrelated to study intervention.
- **Possibly Related**: There is some temporal relationship between the event and the administration of the study intervention, and the event is unlikely to be explained by the participant's medical condition or other therapies.
- **Probably Related**: The temporal relationship between the event and administration of the study intervention is suggestive and the event is unlikely explained by the participant's medical condition or other therapies.
- **Definitely Related**: The event follows reasonable temporal sequence from administration of the study intervention, follows a known or suspected response pattern to the study intervention, is confirmed by improvement upon stopping the study intervention, and reappears upon repeated exposure, if that occurs.

10.4.4.4. Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated, or as requested by Sponsor and/or Medical Monitor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the SAE coordinator within 24 hours of receipt of the information.

10.4.5. Reporting of SAEs

Facsimile or electronic transmission of the SAE Report Form is the preferred method to transmit this information to the SAE Submission Coordinator.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE Report Form within the designated reporting time frames.

Contacts for SAE reporting can be found on page 3.

10.5. Appendix 5: Contraceptive and Collection of Pregnancy Information

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from Day 1 through 12 weeks after the last dose of study intervention:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year, as described in Table 7, when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

Male participants must refrain from donating sperm for the duration of the study and for 12 weeks after the last dose of study intervention.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse, or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly throughout the study and for 12 weeks following the last dose of study intervention, as described in Table 7.

Table 7: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of < 1% per year when used consistently and correctly.***
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – Oral – Intravaginal – Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation – Oral – Injectable
Highly Effective Methods That Are User Independent [a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation – Intrauterine device (IUD) – Intrauterine hormone-releasing system (IUS) – Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method, provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[a] Typical-use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Note: In Japan, contraceptive drugs or devices used must be approved or certified in Japan.

10.5.3. Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test. Positive urine tests should be confirmed with a serum test.
- Additional pregnancy testing should be performed at monthly intervals during the treatment period and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed 2 to 3 weeks after administration of the last dose of study intervention in any WOCBP who prematurely discontinues the study.
- Pregnancy testing with a sensitivity of at least 10 mIU/mL will be performed.

10.5.4. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the

study intervention by the Investigator will be reported to the Sponsor as described in Section 10.4.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

All participants will be monitored for possible signs of DILI. Safety laboratories will be monitored by a central laboratory in real time with potential DILI alerts sent to the Investigator.

PARTICIPANTS AGED ≥ 6 YEARS OF AGE

For participants with normal liver biochemistries at baseline:

- **Close Monitoring:** An increase of serum ALT or AST to > 3 x ULN should be followed by repeat testing of ALT, AST, alkaline phosphatase, and total bilirubin within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry should also be made about symptoms, strenuous exercise, or previous seizures. Repeat testing 2 or 3 times weekly is recommended. All participants showing possible DILI should be followed until abnormalities return to normal or to the baseline state. If a participant lives remote from the study site, local testing may be performed, and the test results reported to the Investigator (along with the reference ranges for the local laboratory).
- **Study Intervention Discontinuation:** Study intervention will be discontinued when a participant meets one of the conditions outlined below (from 2009 FDA Guidance for Industry-Drug Induced Liver Injury: Premarketing Clinical Evaluation) or if the Investigator believes that it is in best interest of the participant.
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

For participants with elevated transaminases at baseline:

The following Alternative DILI Monitoring Algorithm should be used.

- **Close Monitoring**: If participants develop elevations of AST or ALT > 2 times baseline or total bilirubin > 1.5 times baseline while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2 to 3 times per week, with or without study intervention discontinuation (see below).
- **Study Intervention Discontinuation:** Study intervention will be discontinued for abnormal liver function when a participant meets the following condition:
  - ALT or AST > 5 × baseline, with baseline < 2 × ULN

Close monitoring should be continued. If a participant lives remote from the study site, local testing may be performed, and the test results reported to the Investigator (along with the reference ranges for the local laboratory).

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the SoA.

Participants should be monitored at each study visit and instructed to call the Investigator for new or worsening symptoms of clinical hepatitis. Both symptoms and calls should be captured in dedicated case report forms.

PARTICIPANTS AGED < 6 YEARS OF AGE

Close Monitoring

For participants with normal liver biochemistries at baseline:

- An increase of serum ALT or AST to > 3 × ULN should be followed by repeat testing of ALT, AST, alkaline phosphatase, and total bilirubin within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry should be also made about symptoms, strenuous exercise, viral infections, or previous seizures. Repeat testing 2 or 3 times weekly is recommended. All participants showing possible DILI should be followed until abnormalities return to normal or to the baseline state.

For participants with elevated transaminases at baseline the following Alternative DILI Monitoring Algorithm should be used:

- If participants develop elevations of AST or ALT > 2 times baseline or total bilirubin > 1.5 times baseline while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2 to 3 times per week.

Study Intervention Interruption/Discontinuation

Study drug must be interrupted if any of the following criteria are met (applies to participants with normal and elevated transaminases at baseline):

- ALT or AST > 8 x ULN
- ALT or AST > 5x ULN for 2 weeks or longer
- ALT or AST > 3 x ULN in association with total bilirubin > 2x ULN and/or clinical jaundice or other signs of liver dysfunction (hepatomegaly, pruritus, bleeding, etc).

As children can have LFT elevation from viral infections and medications, an investigation of potential alternative causes (acetaminophen use, EBV, CMV infection, etc) and physical examination should be conducted, and the participant should be closely monitored for clinical progression. **If no alternative etiology is identified, the participant should be discontinued from the study, even if the participant has a normal physical exam.**

If an alternative, reversible cause of transaminase elevation has been identified, and the physical examination is normal the medical monitor should be consulted, and study drug may be resumed after the investigator has confirmed the participant's clinical stability and the transaminases are back to < 2 x ULN. Transaminases and bilirubin should be monitored at least weekly for 4 weeks after resuming study drug. **If a protocol defined transaminase elevation (> 3 x ULN for participants with normal baseline or > 2 x baseline for those**

with elevated baseline) recurs after re-challenge with the study drug the study drug should be permanently discontinued, regardless of the etiology.

If a participant lives remote from the study site, local testing may be performed, and the test results reported to the Investigator (along with the reference ranges for the local laboratory).

Participants should be monitored at each study visit and instructed to call the Investigator for new or worsening symptoms of clinical hepatitis and/or liver dysfunction. Both symptoms and calls should be captured in dedicated eCRFs.

10.7. Appendix 7: Abbreviations

Term	Definition
abs	absolute
ADA	anti-drug antibody
AE	adverse event
AESI	AE of special interest
AGXT	the gene that codes for alanine–glyoxylate aminotransferase
aHR	adjusted hazard ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-dsDNA	anti-double-stranded DNA antibody
ASE	American Society of Echocardiography
AST	aspartate aminotransferase
ASGPR	asialoglycoprotein receptor
AUC	area under the curve
AUC_{∞}	area under the concentration-time curve from time zero to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t.
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase (creatine phosphokinase)
CKD	chronic kidney disease
cm	centimeters
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology for Adverse Events
DCR-L1360	drug substance for this IMP
DCR-PHXC	drug product for this IMP
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic CRF
EFD	embryofetal development
e.g.	for example

Term	Definition
eGFR	estimated glomerular filtration rate
EOS	End of Study
ER	emergency room
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESPN	European Society of Pediatric Nephrology
ESRD	end-stage renal disease
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GalNAc	*N*-acetyl-D-galactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
GO	glycolate oxidase
GRHPR	the gene that codes GRHPR
HIPAA	Health Insurance Portability and Accountability Act
HOGA	4-hydroxy-2-oxoglutarate aldolase
HOGA1	gene that codes for HOGA
hr	hour(s)
HRQOL	Health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonisation)
i.e.	that is
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
IWRS	Interactive Web Response System
kg	kilogram(s)
LDH	lactate dehydrogenase
LDHA	primate (human and nonhuman) lactate dehydrogenase type A
LDHA	the gene that encodes LDHA
Ldha	the gene that encodes LDHA in mice
LFT	liver function test(s)
M&S	modeling and simulation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

Term	Definition
MITT	modified intent-to-treat population
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
mRNA	messenger ribonucleic acid
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NIMP	non-investigational medicinal product
NMD-PH	no-mutation-detected primary hyperoxaluria
PCP	primary care physician
PD	pharmacodynamic(s)
PE	physical examination
PedsQL™	Pediatric Quality of Life Inventory
PH	primary hyperoxaluria
PH1	primary hyperoxaluria type 1
PH2	primary hyperoxaluria type 2
PH3	primary hyperoxaluria type 3
PK	pharmacokinetic(s)
Pox	plasma oxalate
PT	prothrombin time
QoL	quality of life
QTcF	QT interval (Fridericia correction)
RNA	ribonucleic acid
RNAi	RNA interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
siRNA	small interfering RNA
SoA	schedule of activities
SOC	system organ class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
Uox	urinary oxalate excretion
WFI	water for injection
WHO	World Health Organization
WOCBP	women of childbearing potential
WPAI:PH, V2.0, CPV	Work Productivity and Activity Impairment Questionnaire: Primary Hyperoxaluria V2.0, Clinical Practice Version

10.8. Investigator Signature Page

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 Number: DCR-PHXC-203

Version: 4.0

Date: 23-Feb-2023

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and local regulations (as applicable).

Signature	**Date**
Name:	
Institution:	**Site Number:**

10.9. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 2, version 3.0 (01-Nov-2022)

The 21-Dec-2021 version of the protocol was amended to expand the population to include <2-year-old participants.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
2.2.3 Clinical Overview 4.1 Overall Design 9.6 Safety Review Committee (SRC)	Expanded population to include 0- to 2-year-old participants.	The SRC performed the protocol-specified review of safety data to allow enrollment of children from birth to 2 years in the study population.
2.2.3 Clinical Overview	Added results for DCR-PHXC-201 and DCR-PHXC-104 and included updates for DCR-PHXC-301 and DCR-PHXC-204.	To provide updated information on completed and ongoing studies.
1.1 Synopsis	Updated the key inclusion criteria for consistency with those listed in Section 5.1	To correct previously omitted text.
1.3 Schedule of Activities	Corrected errors in the SoA relating to recording of fluid intake.	No recording of fluid intake is needed on Day 1. Fluid intake should be recorded in case of early termination.
Sponsor Signature Page	Updated to replace previous signatory.	To account for Sponsor personnel changes.
Medical Monitor and Pharmacovigilance Contact Information	Updated for accuracy with current personnel contact information.	To account for Sponsor personnel changes.

Amendment 1, version 2.0 (21-Dec-2021)

The 15-Apr-2021 version of the protocol was amended to expand the population to include 6- to 11-year-old participants. Other principal changes included changing the primary objective from safety to efficacy, adding pregnancy and contraception requirements, adding a maximum dose of 170 mg, updating the number of planned participants from 15 to 25, and clarifying that the efficacy endpoints will be presented by PH1, PH2, or PH3 subgroups.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Title Page Sponsor Signature Page 1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities 2.1. Study Rationale 3. Objectives and Endpoints 4.1. Overall Design 4.2. Scientific Rationale for Study Design 4.3.1. PK/PD Model for Dose Selection in Pediatric Participants (Birth to 11 Years) 5.1. Inclusion Criteria 6.2.1. Handling and Accountability 6.2.3. Preparation and Administration 6.4. Study Intervention Compliance 7.1.1. Discontinuation of Study Intervention Stopping Rules for Individual Participants 8.1.4.1. Pediatric Quality of Life Inventory 8.3.5. Pregnancy 9.2. Sample Size Determination 9.6. Safety Review Committee (SRC) 10.2. Appendix 2: Clinical Laboratory Tests 10.4. Appendix 4: Contraceptive and Collection of Pregnancy Information (New) 10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments 10.7. Investigator Signature Page	Expanded population to include 6- to 11-year-old participants: 1. Updated Study title and study description 2. Updated average spot Uox-to-creatinine ratio inclusion criteria to include values for 6 to 11 year olds 3. Removed word the word ‘young’ from the phrase ‘in neonates, infants, and young children with PH’ 4. Added in details regarding dose selection for 6- to 11-year-olds 5. Clarified that 6- to 11-year-olds may have home dosing performed by caregivers or home nurses 6. Updated QoL assessment text to account for 6- to 11-year-olds 7. Clarified that is still required to have 60 days’ worth of data from children aged 2 to 5 years old prior to enrolling participants < 2 years 8. Updated liver safety suggested actions and follow-up 9. Added contraception and pregnancy guidelines	1. To update upper age limit to 11 years of age 2. To account for the correct values for 6- to 11-year-olds 3. Children up to 11 years old can now be enrolled 4. Although the dose is the same, the dose selection for 6- to 11-year-olds was separate from the 0 to 5 year olds 5. For older children, it may be possible for caregivers to administer the study drug at home. 6. To account for the questionnaires to be used by 6- to 11-year-olds 7. For participant safety, it is required to review data from children aged 2 to 5 prior to enrolling participants < 2 years 8. Added liver safety suggested actions and follow-up for 6- to 11-year-olds 9. To account for 6- to 11-year-olds who may be of childbearing potential
1.1. Synopsis 3. Objectives and Endpoints 4.2. Scientific Rationale for Study Design 9.4.2. Primary Endpoints 9.4.3.1. Efficacy Endpoints	Updated the primary endpoint to efficacy based upon spot urinary oxalate-to-creatinine ratio; safety endpoint was moved to secondary	To support regulatory objectives for the DCR-PHXC clinical development program

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1. Overall Design 4.3.1. PK/PD Model for Dose Selection in Pediatric Participants (Birth to 11 Years) 6.1. Study Intervention(s) Administered	Added a maximum dose of 170 mg	To ensure the dose in children does not exceed the maximum dose given to adult participants across the program
6.1. Study Intervention(s) Administered	Clarified for participants ≥ 6 months of age at Screening, the dose will remain constant throughout the study (i.e., the dose administered on Day 1 will be the dose administered at all following visits regardless of any change in body weight)	Clarification
1.1. Synopsis 1.2. Schema 4.1. Overall Design 9.2. Sample Size Determination	Updated number of planned participants from 15 to 25: 1. Added new number of expected participants aged 6 to 11 years old 2. Added goal of enrolling approximately 15 participants with PH1	1. To account for additional participants aged 6 to 11 years old 2. To help achieve regulatory goals related to PH1
1.2. Schema 1.3. Schedule of Activities	Clarified in the schedule of activities table that 12-lead ECG should be assessed at Day 30 (noted in Administrative Letter 1, dated 07 June 2021)	Clarification
5.1. Inclusion Criteria	Corrected the inclusion criterion related to serum creatinine cut off for participants aged less than 12 months to be below the 97.**5**th percentile of a healthy population (noted in Administrative Letter 3, dated 07 July 2021)	This inclusion criterion is based upon the Boer et al 2010 article, which presents the 97.**5**th percentile serum creatinine
1.1. Synopsis 3. Objectives and Endpoints 9.4.3.1. Efficacy Endpoints	Clarified that the secondary efficacy endpoint related to normalization of spot urinary oxalate-to-creatinine ratio includes participants with spot urinary oxalate-to-creatinine ratio ≤ the ULN **or** ≤ 1.5 x ULN at any time point	This endpoint will include the percentage of participants who had spot urinary oxalate-to-creatinine ratio ≤ the ULN **or** ≤ 1.5 x ULN

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities 2.3.2. Pediatric Burden Assessment 8.2.5. Echocardiogram with Doppler	Clarified that if for an individual participant the echocardiogram cannot be performed without sedation, the echocardiogram should not be performed (noted in Administrative Letter 4, dated 20 August 2021)	The intent of the protocol is that the echocardiogram will not involve any invasive procedures
2.3.4. Risk Management	Clarified details surrounding the SRC review	Clarification
2.1. Study Rationale 2.2.3.1. Clinical Studies of Nedosiran	Added preliminary findings from Study DCR-PHXC-201 and status updated of Study DCR-PHXC-104	To provide updated information
4.1. Overall Design	Clarified that a substantial amendment will be submitted when the data are available to support enrollment for applicable cohorts before any participants < 2 years of age are enrolled.	Clarification
6.5. Concomitant Therapy	Clarified that the requirement to have a stable dose of pyridoxine for 3 months prior to the study did not apply to those under 3 months of age; for such participants, the timeframe requirement for stable dose is relative to their age	It is not possible for participants under 3 months of age to have had a stable dose for at least 3 months
Title Page	Added the EudraCT Number (noted in Administrative Letter 2, dated 09 June 2021) and the NCT Number	Newly available
2.1. Study Rationale 2.2.3.1. Clinical Studies of Nedosiran	Added preliminary findings from Study DCR-PHXC-201 and status updated of Study DCR-PHXC-104	To provide updated information
2.2.1. Overview of Primary Hyperoxaluria	Clarified that systemic oxalosis can occur in patients with PH3	Newly available literature
1.1. Synopsis 3. Objectives and Endpoints 9.4.2. Primary Endpoint 9.4.3.1. Efficacy Endpoints 9.4.4. Tertiary/Exploratory Endpoint(s)	Clarified that the efficacy endpoints will be presented by PH1, PH2, or PH3 subgroups	To allow analysis of the PH subtypes separately
1.3 Schedule of Activities 8.9. Immunogenicity Assessments	Removed text that stated blood samples for analysis of ADA will be analyzed once a validated methodology is available	The ADA assay is now fully validated

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.2.2. Physical Examinations	Clarified text regarding physical examination to ensure the physical examination is conducted according to the schedule of activities table	Clarification
8.5. Pharmacokinetics	Removed reference to blood samples collected for measurement of plasma concentrations of nedosiran metabolites	Concentrations of nedosiran metabolites will not be measured from blood samples
2.1. Study Rationale 2.2.1. Overview of Primary Hyperoxaluria	Clarified that a treatment for PH1 has been approved in a limited number of countries	Clarification
1.3. Schedule of Activities 8.1.5. Reporting Fluid Intake	Throughout the protocol, the text 'non-breastfeeding' was updated to 'non-breastfed'	This text is referring to a child that is breastfed
6.5.3. COVID-19 and other Vaccines Administration	Updated text to clarify that no vaccines should be administered in the 7 days prior to or following scheduled administration of study intervention	To allow discernment of AEs related to the administration of other vaccines from those related to administration of study intervention
9.6. Safety Review Committee (SRC)	Added an ethicist as a member of the SRC	To add an additional member given the age of the study population
10.1.1. Regulatory and Ethical Considerations	Corrected the CIOMS International Ethical Guidelines reference to CIOMS **VI**, 2005	Corrected an error in the previous version of the protocol that referred to the guidance as CIOMS IV
10.1.1. Regulatory and Ethical Considerations	Clarified that applicable privacy laws will be followed	For protection of participant privacy
10.1.3. Informed Consent Process	Added language stating participants must be informed of any new information that arises during the course of the study which might be relevant to their willingness to continue in the study and addressed changes in age related to ICF and clarified that as children and adolescents age, they must be re-consented to the appropriate ICF based on current age	To ensure participants are provided with necessary information to make an informed decision about continuing participation in the study
Protocol Amendment Summary of Changes 10.8. Protocol Amendment History	New section added to describe amendment summary of changes	To accommodate amendment summary of changes
Additional editorial changes and minor clarifications were made throughout the protocol.		

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