Primary hyperoxaluria (PH) is a family of ultra-rare autosomal recessive inherited disorders of hepatic glyoxylate metabolism characterized by oxalate overproduction. Nedosiran is an RNA interference agent that inhibits hepatic lactate dehydrogenase, the enzyme responsible for the common, final step of oxalate production in all three genetic subtypes of PH. Here, we assessed in a two-part, randomized, single-ascending-dose, phase 1 study (PHYOX1) the safety, pharmacokinetics, pharmacodynamics, and exposure-response of subcutaneous nedosiran in 25 healthy participants (Group A) and 18 patients with PH1 or PH2 (Group B). Group A received nedosiran (0.3, 1.5, 3.0, 6.0, then 12.0 mg/kg) or placebo, and Group B received open-label nedosiran (1.5, 3.0, or 6.0 mg/kg). No significant safety concerns were identified. Injection site reactions (four or more hours post dose) occurred in 13.3% of participants in Group A and 27.8% of participants in Group B. Mean maximum reduction in 24-hour urinary oxalate excretion from baseline to day 57 (end of study) across Group B dose cohorts was 55% (range: 22%–100%) after single-dose nedosiran, with 33% participants reaching normal 24-hour urinary oxalate excretion. Based on the available modeling and simulation data, a fixed monthly dose of nedosiran 160 mg (free acid; equivalent to 170 mg sodium salt) in adults was associated with the highest proportion of simulated individuals achieving normal or near-normal 24-hour urinary oxalate excretion and fewest fluctuations in urinary oxalate response. Thus, single-dose nedosiran demonstrated acceptable safety and evidence of a pharmacodynamic effect in both PH1 and PH2 subpopulations consistent with its mechanism of action.

Kidney International (2021) (null), 1-11; https://doi.org/10.1016/j.kint.2021.08.015

KEYWORDS: chronic kidney disease; gene expression; hyperoxaluria; pediatric nephrology; pharmacokinetics; urology

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Primary hyperoxaluria (PH) represents a family of ultrarare autosomal recessive inherited disorders of hepatic glyoxylate metabolism characterized by overproduction of oxalate, a metabolic end product eliminated almost exclusively by the kidneys.1,2 In PH, excessive urinary oxalate (Uox) excretion engenders calcium oxalate precipitation, leading to nephrocalcinosis, recurrent urolithiasis, and kidney damage.1–3 Progression to kidney failure occurs over months to years and may be associated with systemic oxalosis and multiple organ failure.1,2,4–9

PH encompasses 3 related but genetically distinct subtypes (PH1, PH2, and PH3), each characterized by a specific enzyme deficiency, resulting in increased levels of intrahepatocellular glyoxylate.1,2,10–12 Nearly all intrahepatocellular glyoxylate undergoes conversion to oxalate by hepatic lactate dehydrogenase (LDH), a homotetrameric enzyme encoded by the LDHA gene.1,3 In PH1, kidney failure occurs in 19% and 57% of patients by the ages of 10 and 40 years, respectively,7,8 whereas infantile oxalosis, resulting in early death, may occur in up to 5% of cases.7,9 More than one-third of patients with PH2 progress to kidney failure by the age of 40 years.14 More than half of PH3
cases (50%–89%) present with renal stones before the age of 5 years,15,16 14% to 29% develop chronic renal disease,16–18 and 3% to 4% develop kidney failure by the age of 40 years.8,16

Novel therapeutic strategies focus on RNA interference (RNAi) to decrease the levels of enzymes involved in the glyoxylate metabolic pathway and so reduce oxalate production. One such RNAi therapeutic, lumasiran (Alnylam Pharmaceuticals, Inc.), depletes an enzyme (hydroxyacid oxidase 1) responsible for glyoxylate synthesis.19 Because of its mechanism of action, lumasiran is only approved for use in patients with PH1.

Nedosiran is an investigational RNAi therapeutic composed of nedosiran sodium (a synthetic, double-stranded RNAi oligonucleotide conjugated to N-acetyl-D-galactosamine amino sugar residues). The N-acetyl-D-galactosamine amino sugar residues ensure preferential uptake by hepatocytes via the asialoglycoprotein receptor. After hepatocyte internalization and release into the cytoplasm, nedosiran exploits the endogenous RNAi regulatory mechanism to degrade LDHA mRNA, thereby reducing production of the LDHA protein.20 Consequently, the activity of hepatic LDH, the key common enzyme involved in the final conversion of glyoxylate to oxalate in all 3 known genetic subtypes of PH, is reduced (Figure 1).20–25 Nonclinical data have shown marked reduction of Uox excretion after RNAi treatment targeting hepatic LDHA mRNA, with no evidence of off-target laboratory or clinical effects.

A first-in-human, phase 1 study (DCR-PHXC-101; PHYOX1) of nedosiran was conducted in healthy volunteers and patients with PH1 or PH2. The primary objective was to evaluate the safety and tolerability of single, ascending doses of nedosiran. Secondary objectives were to characterize the pharmacokinetics (PKs) and pharmacodynamics (PDs) of a single dose of nedosiran. The PK and PD data obtained from this study were used in modeling and simulations to select a dose and dosing regimen for future clinical studies.

METHODS

Study design and conduct

PHYOX1 was a 2-part, single-ascending-dose, phase 1 study of nedosiran s.c. injection in healthy volunteers (Group A, N = 25) and patients with PH1 or PH2 (Group B, N = 18) conducted between November 2017 and November 2019 (ClinicalTrials.gov number: NCT03392896). Group A received, in a randomized, participant-blind manner, 1 of 5 dose levels of nedosiran or matching placebo in a 3:2 ratio at a single site in the United Kingdom (Supplementary Figure S1). Once safety was established in Group A by an independent safety review committee (SRC), Group B commenced randomized treatment at 1 of 3 single-dose levels of open-label, s.c. nedosiran (Group B lagging Group A by at least 1 dose-level cohort; Supplementary Figure S2). The study of Group B was conducted at 4 sites in the European Union and 1 site in the United States.

The study protocol was designed jointly by the investigators and sponsor (Dicerna Pharmaceuticals, Inc.) and approved by institutional review boards or local ethics committees. The study was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Written informed consent was obtained from all adult participants and the parents or legal guardians of participating children; children assented as appropriate. The SRC convened at predefined decision points and the occurrence of any potential dose-limiting toxicities to ensure the acceptability of continued nedosiran administration within each cohort and of dose escalation to subsequent cohorts. Full details of the methods are provided in the Supplementary Appendix.

Study participants

Healthy, nonsmoking men and women, aged 18 to 55 years, with a body mass index of 19 to 32 kg/m², were eligible for enrollment into Group A.

Key eligibility criteria for enrollment into Group B were age ≥6 years (≥18 years in the Netherlands), a genetically confirmed diagnosis of PH1 or PH2, 24-hour Uox excretion ≥0.7 mmol for patients aged ≥18 years (or ≥0.7 mmol per 1.73 m² body surface area for patients aged <18 years) based on 1 of 2 measurements at screening (with <30% variation between both measurements), and an estimated glomerular filtration rate ≥30 ml/min per 1.73 m², calculated using the Modification of Diet in Renal Disease formula in adults or the formula by Schwartz in patients aged 6 to <18 years.27–29 Patients with PH1 receiving pyridoxine at stable doses ≥4 weeks before study entry must have been willing and able to remain on the same stable dose during the study. Key Group B exclusion criteria were prior renal and/or hepatic transplantation, current dialysis, systemic oxalosis, and liver function test abnormalities.

Interventions

The test drug was a sterile solution containing nedosiran, 160 mg/ml (free acid; equivalent to 170 mg/ml sodium salt, manufactured by Dicerna Pharmaceuticals, Inc.). Nedosiran is an RNA that is isolated as its sodium salt; the dosing data in this article are expressed as the sodium salt. Placebo was normal saline (0.9%) solution for s.c. injection with similar osmolality to the test drug. In an attempt to show pharmacologic proof of concept in healthy volunteers, Group A received a gelatin-loaded breakfast (20 g gelatin), with the goal of increasing plasma and urinary levels of oxalate and glycolate.30

Study treatment

On day 0 (baseline), Group A ingested a gelatin load before initiating a 24-hour urine collection. Participants in Group A were then assigned to single-dose cohorts of sequentially higher-dose levels of nedosiran (0.3, 1.5, 3.0, 6.0, or 12 mg/kg) or placebo on day 1. The first 2 participants (sentinels) in each dose-level cohort were dosed on the same day with either nedosiran or placebo. After being deemed safe and tolerable by the SRC, following a 3-day observation period, the remaining participants in the dose-level cohort were randomized 2:1 to nedosiran or placebo. After all participants in each dose-level cohort had received study intervention, the SRC reviewed ≥8 days of postdose safety and tolerability data before authorizing escalation to the next dose level.

Group B participants with PH1 or PH2 received a single dose of open-label nedosiran, 1.5, 3.0, or 6.0 mg/kg. Once nedosiran was deemed by the SRC to be safe and tolerable in the first patient, following an 8-day observation period, the remaining patients in that dose-level cohort received study treatment. After all patients in each dose level had received study treatment, the SRC reviewed ≥15 days of postdose data to confirm acceptable safety and tolerability before authorizing escalation to the next dose level, provided that safety at
that next dose level had been previously deemed acceptable in Group A. Patients were discharged from the clinical site on day 2 and returned for assessments and monitoring on days 8, 15, 22, 29, and 43 and at the end of the study/day 57.

After the end of the study/day 57, patients in Group B had the opportunity for inclusion and enrollment into the long-term, multiple-dose, open-label extension DCR-PHXC-301 study (PHYOX3; NCT04042402), once the clinical study sites became active. PHYOX3 eligibility initially required a return to the lowest predose screening 24-hour Uox excretion value. If the 24-hour Uox excretion value at the day 57 visit or subsequent follow-up monitoring visit did not return to ≥80% of the lowest predose screening 24-hour Uox excretion value. If the 24-hour Uox excretion value at the day 57 visit or subsequent follow-up monitoring visit did not return to ≥80% of lowest screening value, patients were scheduled for additional follow-up (the return to ≥80% of screening value requirement was later waived via a protocol amendment [Supplementary Table S1]). Any postday 57 visit is referred to as the monitoring phase herein.

Assessments and endpoints
The primary objective of this study was to assess the safety and tolerability of a single dose of nedosiran. Safety was evaluated by adverse event (AE) monitoring, vital sign measurements, physical examinations, laboratory assessments, and 12-lead electrocardiograms. AEs were coded using the Medical Dictionary for Regulatory Activities (version 21.0) and graded according to intensity categories.

Injection site reactions (ISRs) were protocol defined as all AEs at the injection site (e.g., erythema, pain, and swelling) that started ≥4 hours after study drug administration. As ISRs in Group A were recorded on a separate case report form, they were not graded for severity or causality. A retrospective analysis of injection site AEs was conducted to characterize ISRs in Group B.

Serial blood samples were collected predose and at prespecified postdose times to characterize plasma nedosiran PKs. Nedosiran PDs were assessed by changes in Uox over 24-hour periods at baseline and at each postdose visit.

Statistical analysis
The sample size was not based on power calculations. Groups A and B were analyzed separately and not pooled for analysis. All participants who received a dose of nedosiran or placebo were included in the safety analyses. PK (Groups A and B) and PD (Group B) analyses are reported for participants who received nedosiran and had sufficient data for at least 1 postdose PK/PD assessment.

For Group B, summary statistics are presented by PH type for the observed maximal reduction in 24-hour Uox excretion and time to maximal reduction in 24-hour Uox excretion. Change from baseline was the difference between 24-hour Uox excretion at baseline (derived as the average of 2 predose measurements) and at each postdose visit. We determined the percentage of participants with PH1 or PH2 achieving 24-hour Uox excretion of <0.46 mmol per 24 hours (i.e., normal) and ≥0.46 to <0.60 mmol per 24 hours (i.e., ≥1.0 x to <1.3 x the upper limit of normal, herein termed near normal) on the basis of their lowest postdose 24-hour Uox excretion measurement. For participants aged <18 years, 24-hour Uox excretion was adjusted for body surface area.

Exposure-response modeling
A nedosiran population PK/PD model was developed using data collected in PHYOX1 to support a nedosiran dosing strategy in adults who could optimize reductions in 24-hour Uox excretion. A sequential PK/PD modeling approach was used. A population PK model was developed first based on plasma nedosiran concentrations and covariate data. Samples and biometrics from 15 healthy volunteers and 10 patients with PH were used to develop the PK model.

Individual model-predicted exposures were used to perform exposure-response analyses for PD effect (i.e., 24-hour Uox excretion) in the PHYOX1 study. An indirect response model was used to describe 24-hour Uox excretion data. The initial model was built with data from 10 patients with PH1 or PH2 and continues to be updated with data from additional patients from other clinical studies of nedosiran. The modeling and simulation data presented herein derive from the initial model.

For nedosiran dose selection in a multiple-dose setting, a variety of scenarios—including different weight-based doses, different intervals between doses, loading dose, maintenance dose strategy, and fixed-dosing strategy—were simulated on the basis of the final population PK/PD model.

For each dosing regimen, the proportions of simulated subjects with a 24-hour Uox excretion <0.60 mmol (near-normal and normal range) and <0.46 mmol (normal range) at 13, 26, 39, and 52 weeks were tabulated. In addition, the simulations in adults were stratified by the extremes of body weight (5th and 95th percentiles) to assess the impact of body weight on 24-hour Uox excretion response.

RESULTS
Study population
All 25 participants in Group A and all 18 patients in Group B completed the scheduled end of the study visits at days 29 and 57, respectively (Supplementary Figure S3). Demographics and baseline characteristics are shown in Supplementary Table S2 for Group A and Table 1 for Group B. Of the 18 patients in Group B, 15 (83.3%) had PH1 and 3 (16.7%) had PH2.
Safety

There was no treatment- or dose-related trend in the frequency or severity of AEs or in clinically significant findings in clinical laboratory parameters, vital signs, 12-lead electrocardiograms, or physical examinations over the entire postdose observation period. No participant withdrew prematurely from the study. No dose-limiting toxicities occurred in Group A or B.

In Group A, treatment-emergent AEs were reported in 4 of 15 nedosiran-treated participants (26.7%), none of which were considered serious (Supplementary Tables S3 and S4). All AEs in the nedosiran arm of Group A were mild to moderate in severity. Two ISRs occurred in 2 of the 15 (13.3%) Group A participants treated with nedosiran. Because no safety concerns were identified in Group A by the SRC, the dose-escalation schedule for nedosiran in Group B commenced.

AEs were reported in 17 of 18 patients (94.4%) receiving nedosiran in Group B (Table 2 and Supplementary Table S5). Of these patients, 11 (61.1%) had AEs that were considered treatment-related (Table 3). The most frequent treatment-related AEs were classified under system organ class ‘general disorders and administration site conditions’ and occurred in 7 of 18 patients (38.9%), with 5 patients (27.8%) having ISRs. These ISRs were characterized by mild-to-moderate erythema and resolved spontaneously within 25 hours from onset. Four patients had a total of 5 serious AEs (pyelonephritis [n = 2], ureterolithiasis [n = 2], and appendicitis [n = 1]), none of which was considered related to nedosiran. Of 18 patients, 3 (16.7%) had AEs that were considered severe (flank pain, appendicitis, and urinary calculus), none of which was considered treatment-related.

PK profile

In Groups A and B, median time to maximal nedosiran plasma concentration occurred 6 to 12 hours after administration (Supplementary Table S6), and the elimination half-life of nedosiran in plasma after a single dose ranged from 4.6 to 13.8 hours. In Group B, a 4.0-fold increase in dose (from 1.5 to 6.0 mg/kg) led to a 3.8-fold increase in peak plasma nedosiran concentration and a 4.2-fold increase in area under the plasma nedosiran concentration-time curve from time of administration to 24 hours, indicating linear PKs across this dose range.

PD data

Gelatin loading did not result in sufficient increases in Uox in Group A to allow for detectable lowering after study drug administration (Supplementary Figure S4).

After administration of single-dose nedosiran in Group B, the mean maximum percentage reduction in 24-hour Uox excretion from baseline to day 57 across dose-level cohorts was 55.0% (range, 22%–100%) and the mean (SD) time to maximum reduction was 45.9 (9.5) days, with a trend toward a greater reduction with increasing dose (Table 4 and Figure 2). The evolution of 24-hour Uox excretion in each individual within the 3 dose-level groups is shown in

### Table 1 | Baseline demographics and clinical characteristics for patients with PH type 1 or 2 (Group B), stratified by nedosiran dose level

| Status | 1.5 (n = 6) | 3.0 (n = 8) | 6.0 (n = 4) | Nedosiran overall (N = 18) |
|--------|------------|------------|------------|--------------------------|
| **Age, yr** | | | | |
| Mean (SD) | 26.5 (9.40) | 25.4 (6.72) | 16.5 (3.51) | 23.8 (7.94) |
| Median (range) | 24.0 (19–45) | 25.5 (16–38) | 16.5 (13–20) | 23.5 (13–45) |
| ≥12 to <18, n (%) | 0 | 1 (12.5) | 2 (50.0) | 3 (16.7) |
| ≥18, n (%) | 6 (100) | 7 (87.5) | 2 (50.0) | 15 (83.3) |
| **Sex, n (%)** | | | | |
| Male | 3 (50.0) | 4 (50.0) | 2 (50.0) | 9 (50.0) |
| Female | 3 (50.0) | 4 (50.0) | 2 (50.0) | 9 (50.0) |
| **Race, n (%)** | | | | |
| White | 4 (66.7) | 4 (50.0) | 3 (75.0) | 11 (61.1) |
| Other | 2 (33.3) | 4 (50.0) | 1 (25.0) | 7 (38.9) |
| British Asian | 1 (16.7) | 0 | 0 | 1 (5.6) |
| Pakistani | 0 | 1 (12.5) | 0 | 1 (5.6) |
| Not reportedb | 1 (16.7) | 3 (37.5) | 1 (25.0) | 5 (27.8) |
| **BMI, kg/m²** | | | | |
| Mean (SD) | 28.74 (3.531) | 21.99 (3.718) | 22.81 (3.068) | 24.42 (4.584) |
| Median (range) | 29.11 (23.98–33.64) | 22.86 (15.15–25.83) | 21.56 (20.80–27.32) | 24.42 (15.15–33.64) |
| **PH type, n (%)** | | | | |
| PH1 | 5 (83.3) | 6 (75.0) | 4 (100) | 15 (83.3) |
| PH2 | 1 (16.7) | 2 (25.0) | 0 | 3 (16.7) |
| **eGFR, ml/min per 1.73 m²** | | | | |
| Mean (SD) | 72.31 (18.220) | 77.45 (28.070) | 106.34 (23.513) | 82.16 (26.493) |
| Median (range) | 74.47 (41.20–94.30) | 75.30 (32.87–113.04) | 105.86 (83.35–130.30) | 80.73 (32.87–130.30) |

BMI, body mass index; eGFR, estimated glomerular filtration rate; PH, primary hyperoxaluria.

aDoses are expressed in terms of the nedosiran sodium salt.

bBecause of privacy restrictions, some sites did not report race.
Table 2 | Summary of treatment-emergent adverse events in patients with primary hyperoxaluria type 1 or 2 (Group B) who received single, ascending doses of s.c. nedosiran

| Variable                                                   | 1.5 (n = 6) | 3.0 (n = 8) | 6.0 (n = 4) | Nedosiran overall (N = 18) |
|------------------------------------------------------------|-------------|-------------|-------------|---------------------------|
| Adverse events, n                                          | 25          | 84          | 41          | 160                       |
| Event, n (%)                                               |             |             |             |                           |
| Any                                                        | 5 (83.3)    | 8 (100)     | 4 (100)     | 17 (94.4)                 |
| Treatment-related                                          | 5 (83.3)    | 4 (50.0)    | 2 (50.0)    | 11 (61.1)                 |
| At injection site<sup>b</sup>                              | 2 (33.3)    | 3 (37.5)    | 2 (50.0)    | 7 (38.9)                  |
| Injection site reaction<sup>c</sup>                        | 1 (16.7)    | 2 (25.0)    | 2 (50.0)    | 5 (27.8)                  |
| Dose-limiting toxicity                                     | 0           | 0           | 0           | 0                         |
| Serious                                                    | 0           | 2 (25.0)    | 2 (50.0)    | 4 (22.2)                  |
| Disease progression<sup>d</sup>                            | 0           | 2 (25.0)    | 1 (25.0)    | 3 (16.7)                  |
| Leading to discontinuation                                 | 0           | 0           | 0           | 0                         |
| Death                                                      | 0           | 0           | 0           | 0                         |

<sup>a</sup>Doses are expressed in terms of the nedosiran sodium salt.
<sup>b</sup>Adverse events at injection sites were all such events that occurred after the dose of study drug, including injection site reactions.
<sup>c</sup>Injection site reactions were all adverse events at injection sites that started ≥4 hours after the first dose of study drug.
<sup>d</sup>Disease progression events were either stone events or signs and symptoms of systemic oxalosis that occurred after informed consent. Stone events must have met ≥1 of the following criteria: renal stone requiring medical intervention, stone passage with or without hematuria, or renal colic requiring medication. Signs and symptoms of systemic oxalosis included retinal, heart, or skin calcifications.

Supplementary Figure S5. Normal 24-hour Uox excretion (upper limit of normal) was achieved in 6 of 18 patients (33%; 5 of 15 with PH1 and 1 of 3 with PH2). An additional 6 patients with PH1 achieved near-normal 24-hour Uox excretion (defined as ≥1.0× to <1.3× the upper limit of normal).

In Group B, after completion of the day 57 visit, 3 patients did not enter the monitoring phase (2 in the 1.5-mg/kg group

Table 3 | Treatment-related adverse events in patients with primary hyperoxaluria type 1 or 2 (Group B) who received single, ascending doses of s.c. nedosiran

| System organ class preferred term                          | 1.5 (n = 6) | 3.0 (n = 8) | 6.0 (n = 4) | Nedosiran overall (N = 18) |
|------------------------------------------------------------|-------------|-------------|-------------|---------------------------|
| Patients with ≥1 event                                     | 5 (83.3)    | 4 (50.0)    | 2 (50.0)    | 11 (61.1)                 |
| General disorders and administration site conditions       | 2 (33.3)    | 3 (37.5)    | 2 (50.0)    | 7 (38.9)                  |
| Injection site erythema                                    | 1 (16.7)    | 2 (25.0)    | 2 (50.0)    | 5 (27.8)                  |
| Injection site pain                                        | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Injection site paresthesia                                 | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Injection site pruritus                                    | 0           | 1 (25.0)    | 0           | 1 (5.6)                   |
| Injection site reaction<sup>c</sup>                        | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| Injection site urticaria                                   | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Fatigue                                                    | 0           | 1 (25.0)    | 0           | 1 (5.6)                   |
| Investigations                                             | 2 (33.3)    | 1 (12.5)    | 1 (25.0)    | 4 (22.2)                  |
| Activated partial thromboplastin time prolonged            | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Blood creatinine increased                                 | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Interleukin level increased                                | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| International normalized ratio increased                   | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Mean cell volume abnormal                                  | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| Weight decreased                                           | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Gastrointestinal disorders                                 | 1 (16.7)    | 1 (12.5)    | 1 (25.0)    | 3 (16.7)                  |
| Nausea                                                     | 1 (16.7)    | 0           | 1 (25.0)    | 2 (11.1)                  |
| Diarrhea                                                   | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Vomiting                                                   | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Nervous system disorders                                   | 1 (16.7)    | 0           | 1 (25.0)    | 2 (11.1)                  |
| Lethargy                                                   | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| Paresthesia                                                | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Infections and infestations                                | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Gingivitis                                                 | 1 (12.5)    | 0           | 0           | 1 (5.6)                   |
| Musculoskeletal and connective tissue disorders            | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Myalgia                                                    | 0           | 1 (12.5)    | 0           | 1 (5.6)                   |
| Respiratory, thoracic, and mediastinal disorders           | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| Epistaxis                                                  | 1 (16.7)    | 0           | 0           | 1 (5.6)                   |
| Skin and s.c. tissue disorders                             | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |
| Urticaria                                                  | 0           | 0           | 1 (25.0)    | 1 (5.6)                   |

<sup>a</sup>Doses are expressed in terms of the nedosiran sodium salt.
<sup>b</sup>Data are expressed as n (%).
and 1 in the 3.0-mg/kg group), as they met the eligibility criteria for PHYOX3 enrollment. The time to achieve these criteria for the remaining 15 patients varied greatly (Supplementary Figure S6).

After taking into account the entire postdose observation period of the study, the nadir of mean maximum percentage reduction in 24-hour Uox excretion across all dose-level cohorts was 64% (range, 28%–100%). The mean time to maximal reduction in 24-hour Uox excretion was 104.6 days (range, 29–348 days). Over the entire postdose observation period, 10 of 18 patients (55.6%; 9 of 15 with PH1 and 1 of 3 with PH2) achieved normal 24-hour Uox excretion, and 4

![Figure 2](image)

Figure 2 | Pharmacodynamic activity of nedosiran in patients with primary hyperoxaluria (PH) type 1 or 2 (Group B). (a) Absolute mean ± SD change in 24-hour urinary oxalate (Uox) excretion from day 0 (D0) to day 57 (D57) in patients with primary hyperoxaluria type 1 or 2 (Group B) who received single, ascending doses of nedosiran (doses expressed in terms of the nedosiran sodium salt). (b) Maximum change for each individual patient up to and including D57. Baseline was defined as the average of the 2 most recent measurements before the first dose of the study drug. After amendment of the protocol, day 22 (D22) was replaced with day 29 (D29). As a consequence, patients recruited early in Group B had assessments performed on D22, whereas patients recruited later had assessments performed on D29. For the purposes of reporting, D22 and D29 data are summarized together (i.e., D22/D29). For patients aged <18 years, the body surface area-adjusted Uox value was summarized. Patients with a reported Uox value below limit of quantification had their 24-hour Uox value set to 0.

### Table 4 | Uox parameters up to day 57 in patients with PH type 1 or 2 (Group B) who received single, ascending doses of nedosiran

| Parameter/population | Nedosiran dose level, mg/kg<sup>a</sup> | Nedosiran overall (N = 18) |
|----------------------|-----------------|--------------------------|
|                      | 1.5 (n = 6)     | 3.0 (n = 8)              |
|                      | 6               | 8                        |
| Overall (PH1 and PH2) | 4               | 4                        |
| No.                  | 18              |
| Maximum Uox reduction from baseline, % | 42.0 (8.9)     | 59.5 (18.5)             |
| Mean (SD)            | 56.4 (27.4)     | 63.1 (35–100)            |
| Median (range)       | 42.3 (28–56)    | 64.0 (22–80)             |
| Time to maximal Uox reduction, d | 48.2 (8.0)     | 41.9 (10.2)             |
| Mean (SD)            | 50.8 (9.0)      | 45.9 (9.5)               |
| Median (range)       | 48.5 (40–57)    | 42.0 (28–56)             |
| Uox normal, n (%)<sup>b</sup> | 0              | 5 (62.5)                |
| Time (D0–D57)        | 1 (100%)        | 2 (100%)                |
| Uox near normal, n (%)<sup>c</sup> | 3 (50.0)       | 1 (25.0)                |
| PH1                  | 0               | 5 (62.5)                |
| Uox normal, n (%)<sup>b</sup> | 0              | 4 (66.7)                |
| Time (D0–D57)        | 1 (100%)        | 2 (100%)                |
| Uox near normal, n (%)<sup>c</sup> | 3 (60.0)       | 1 (16.7)                |
| PH2                  | 1               | 2                        |
| Uox normal, n (%)<sup>b</sup> | 0              | 1 (50.0)                |
| Time (D0–D57)        | 0               | 0                        |
| Uox near normal, n (%)<sup>c</sup> | 0              | 0                        |
| BSA, body surface area; PH, primary hyperoxaluria; ULN, upper limit of normal; Uox, urinary oxalate. | | |
| <sup>a</sup>Doses are expressed in terms of the nedosiran sodium salt. | | |
| <sup>b</sup>Value was <0.46 mmol per 24 hours (corrected for body surface area in patients aged <18 years). | | |
| <sup>c</sup>Value was $0.46 to <0.60 mmol per 24 hours or $1/C2 to <1.3/C2 ULN (corrected for BSA in patients aged <18 years). | | |
additional patients (3 with PH1 and 1 with PH2) achieved near-normal 24-hour Uox excretion.

**Exposure-response and dose selection**

The 24-hour Uox excretion data were best described by an indirect response model in which the nedosiran concentration inhibited the production of Uox. Body weight and estimated glomerular filtration rate were the only 2 covariates that affected exposure (Supplementary Figure S7). Table 5 shows the representative dosing strategies that were simulated. A fixed dose of nedosiran, 170 mg (i.e., 160 mg free acid), once every month had a greater proportion of simulated subjects achieving normal or near-normal 24-hour Uox excretion.

**Table 5 | Percentage of simulated subjects in the normal or near-normal range of 24-hour Uox excretion by nedosiran dosing scenario (representative scenarios)**

| Scenario | Loading dose | Maintenance dose | Week 13 | Week 26 | Week 39 | Week 52 |
|----------|--------------|------------------|---------|---------|---------|---------|
| D        | 3 mg/kg Q1M for 3 doses | 3 mg/kg Q3M starting at month 3 | <0.46 mmol | <0.60 mmol | <0.46 mmol | <0.60 mmol | <0.46 mmol | <0.60 mmol |
| M        | None         | 300 mg Q3M       | 26.0     | 45.9    | 40.0     | 59.5     | 42.4     | 61.7     | 42.8     | 62.1     |
| P        | None         | 170 mg Q1M       | 49.7     | 71.2    | 71.5     | 86.8     | 75.0     | 88.7     | 75.7     | 89.1     |
| Q        | None         | 3 mg/kg Q3M      | 19.1     | 37.2    | 30.1     | 50.4     | 32.3     | 52.5     | 32.7     | 52.9     |

Q1M, every month; Q3M, every 3 months; ULN, upper limit of normal; Uox, urinary oxalate.

Normal Uox excretion range: <0.46 mmol per 24 hours; near-normal Uox excretion range: ≥0.46 to <0.60 mmol per 24 hours or ≥1× ULN to <1.3× ULN. Seventeen scenarios were simulated, including different combinations of weight-based dosing, fixed dosing, loading and maintenance doses, and dosing intervals; doses are expressed in terms of the nedosiran sodium salt. Bold data of Scenario P denote the nedosiran dosing regimen associated with the highest proportion of simulated subjects achieving normal or near-normal 24-hour Uox excretion.
reaching normal or near-normal 24-hour Uox excretion relative to weight-based dosing. The fixed dose of nedosiran, 170 mg (i.e., 160 mg free acid), once monthly was the optimal choice when compared with scenarios assessing higher doses (≈2-fold higher), longer dosing intervals (once every 3 months), and loading regimens. Furthermore, the 24-hour Uox excretion profiles suggest that nedosiran, 170 mg (i.e., 160 mg free acid), given once monthly in adults would have fewer fluctuations in Uox response during the modeled time points (Figure 3). The results were similar regardless of renal function status (normal or mild/moderate impairment).

DISCUSSION
In PHYOX1, all single, ascending doses of nedosiran had an acceptable safety profile in healthy participants and patients with PH1 or PH2. The s.c. injection was well tolerated by all study participants. The most frequent treatment-related AEs were administration site events and ISRs, which is a common occurrence with many s.c. RNAi therapeutics. All ISRs were mild or moderate in severity and resolved spontaneously without treatment.

In patients with PH1 or PH2, PD consistent with the nedosiran mechanism of action was observed as a trend in dose-related reductions of 24-hour Uox excretion coincident with dose-related increases in nedosiran systemic exposure. Because oxalate is primarily produced by hepatic LDH activity, these findings are consistent with nonclinical data showing that nedosiran reaches hepatocytes, where it inhibits LDHA mRNA and thus LDH enzymatic activity. The marked reduction in 24-hour Uox excretion following nedosiran administration in patients with PH1 or PH2 was observed throughout the study duration. Participants in the monitoring phase (postday 57) demonstrated a high degree of variability in 24-hour Uox excretion from visit to visit throughout the course of follow-up. Consequently, the interpretation of these observations is challenging and should not be regarded as an index of an enduring PD effect from a single dose of nedosiran.

Results from PHYOX1 support clinical development of a multiple-dose regimen of nedosiran for the treatment of PH. The exposure-response analyses based on the population PK/PD model supported a fixed nedosiran dose of 160 mg nedosiran (free acid; equivalent to 170 mg sodium salt) once monthly in adults as the dosing regimen associated with the highest proportion of simulated subjects (among the simulated scenarios) achieving and maintaining normal or near-normal 24-hour Uox excretion and the fewest fluctuations in Uox response. Maintaining consistently reduced 24-hour Uox excretion levels should prevent interdose spikes in oxalate levels that could result in acute kidney injury. This dosing strategy is under evaluation in the pivotal, randomized, placebo-controlled PHYOX2 study (NCT03847909 in 35 children and adults with PH1 or PH2) and PHYOX4 study (NCT04555486 in children and adults with PH3), as well as in the long-term extension PHYOX3 study (NCT04042402).

Our findings require confirmation in larger controlled studies. Because the sample size was based on safety rather than efficacy considerations, comparison of the PD response between the PH1 and PH2 subgroups lacks statistical rigor. As 24-hour Uox excretion is an accepted surrogate endpoint for clinical outcomes (e.g., progression of renal dysfunction) in studies of PH7,31,32 the marked reduction in or normalization of 24-hour Uox excretion induced by nedosiran in PH1 and PH2 supports further development of nedosiran for the treatment of PH. Further study is required to evaluate the prognostic association of a decline in 24-hour Uox excretion with kidney outcomes.

In conclusion, this phase 1 study of s.c. nedosiran in healthy volunteers and patients with PH1 or PH2 demonstrated favorable safety and tolerability, predictable PKs, and proof-of-concept PDs. Exposure-response modeling led to the identification of a fixed dose of nedosiran, 160 mg (free acid; equivalent to 170 mg sodium salt), once monthly in adults as the optimal dosing strategy in multiple-dose studies. Targeted therapy that inhibits hepatic LDH activity represents a promising treatment modality for patients with PH regardless of the underlying genetic abnormality.

DISCLOSURE
PC received strategic advisory board fees from Dicerna Pharmaceuticals, Inc., and Alnylam Pharmaceuticals, Inc., during the conduct of the study; and nonfinancial support from OxThera and Advicenne, outside the submitted work. SFG received research grants from Dicerna Pharmaceuticals, Inc., and Alnylam Pharmaceuticals, Inc. JWG received grants from Alnylam Pharmaceuticals, Inc., UniQure Pharmaceuticals, Inc., and Dicerna Pharmaceuticals, Inc.; and speaker fees for primary hyperoxaluria (PH) educational programs and consultant fees from Alnylam Pharmaceuticals, Inc. MAB received scientific advisory board fees from Dicerna Pharmaceuticals, Inc.; speaker fees for PH educational programs and scientific advisory board fees from Alnylam Pharmaceuticals, Inc.; scientific advisory board fees from Orphan Biotech and Chinook; and personal fees from Retrophin; outside the submitted work. CBL received personal fees from Dicerna Pharmaceuticals, Inc., outside the submitted work; and is chair of the Scientific Review Committee for this study. BH was affiliated with the University Hospital Bonn, Bonn, Germany, at the initiation of this study and is currently an employee of Dicerna Pharmaceuticals, Inc. AA and KB are employees of Dicerna Pharmaceuticals, Inc. DM is a paid consultant for Dicerna Pharmaceuticals, Inc. All the other authors declared no competing interests.

DATA STATEMENT
Because of the sensitive nature of the data collected for this study, the data set will not be made available to other researchers. For additional study details, please visit www.clinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT03392896).

ACKNOWLEDGMENTS
We sincerely thank the patients and volunteers who participated in the PHYOX1 (DCR-PHXC-101) study. The study was supported by Dicerna Pharmaceuticals, Inc. (Lexington, MA). The authors acknowledge Ralf Rosskamp, M.D. (formerly of Dicerna Pharmaceuticals, Inc.) and Bob D. Brown, Ph.D. (Dicerna Pharmaceuticals, Inc.) for their invaluable contributions to the
Supplementary References.

Model for nedosiran was an indirect response model.

Figure S6. Level cohort.

Figure S5. Pharmacodynamic activity of nedosiran in individual healthy volunteers (Group A) and patients with primary hyperoxaluria type 1 or 2 (Group B) by dose.

Table S1. Summary of protocol amendments.

Supplementary Results.

Figure S3. Flow of healthy volunteers (A) and patients with primary hyperoxaluria (B) receiving single, ascending doses of nedosiran in PHYOX1.

Table S2. Demographic and baseline characteristics in Group A.

Table S3. Summary of treatment-emergent adverse events in healthy volunteers (Group A) who received single, ascending doses of s.c. nedosiran.

Table S4. Incidence and number of any treatment-emergent adverse event in healthy volunteers (Group A) who received single, ascending doses of s.c. nedosiran.

Table S5. Incidence and number of any treatment-emergent adverse event in patients with primary hyperoxaluria type 1 or 2 (Group B) who received single, ascending doses of s.c. nedosiran.

Table S6. Mean (% CV) plasma pharmacokinetic parameters of nedosiran following single-dose s.c. administration of nedosiran in healthy volunteers (Group A) and patients with primary hyperoxaluria type 1 or 2 (Group B).

Figure S4. Pharmacodynamic activity of nedosiran in healthy volunteers (Group A).

Figure S5. Pharmacodynamic activity of nedosiran in individual patients with primary hyperoxaluria type 1 or 2 (Group B) by dose-level cohort.

Figure S6. Individual 24-hour urinary oxalate excretion status for each monitoring phase visit (Group B).

Figure S7. The final population pharmacokinetic/pharmacodynamic model for nedosiran was an indirect response model.

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