PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2

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Nedosiran is an investigational RNA interference agent designed to inhibit expression of hepatic lactate dehydrogenase, the enzyme thought responsible for the terminal step of oxalate synthesis. Oxalate overproduction is the hallmark of all genetic subtypes of primary hyperoxaluria (PH). In this double-blind, placebo-controlled study, we randomly assigned (2:1) 35 participants with PH1 (n = 29) or PH2 (n = 6) with eGFR ≥30 mL/min/1.73 m^2 to subcutaneous nedosiran or placebo once monthly for 6 months. The area under the curve (AUC) of percent reduction from baseline in 24-hour urinary oxalate (Uox) excretion (primary endpoint), between day 90–180, was significantly greater with nedosiran vs placebo (least squares mean [SE], +3507 [788] vs −1664 [1190], respectively; difference, 5172; 95% CI 2929–7414; $P < 0.001$). A greater proportion of participants receiving nedosiran vs placebo achieved normal or near-normal (<0.60 mmol/24 hours; <1.3 × ULN) Uox excretion on ≥2 consecutive visits starting at day 90 (50% vs 0; $P = 0.002$); this effect was mirrored in the nedosiran-treated PH1 subgroup (64.7% vs 0; $P < 0.001$). The PH1 subgroup maintained a sustained Uox reduction while on nedosiran, whereas no consistent effect was seen in the PH2 subgroup. Nedosiran-treated participants with PH1 also showed a significant reduction in plasma oxalate versus placebo ($P = 0.017$). Nedosiran was generally safe and well tolerated. In the nedosiran arm, the incidence of injection-site reactions was 9% (all mild and self-limiting). In conclusion, participants with PH1 receiving nedosiran had clinically meaningful reductions in Uox, the mediator of kidney damage in PH.

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Primary hyperoxaluria (PH) is a family of 3 ultrarare autosomal recessive disorders (PH1, PH2, and PH3) of enzyme deficiencies in the metabolic pathway of hepatic glyoxylate.[1,2] PH1, PH2, and PH3 are caused by variants in the genes encoding alanine-glyoxylate aminotransferase, glyoxylate reductase/hydroxypyruvate reductase, and 4-hydroxy-2-oxoglutarate aldolase 1, respectively.[3]

In all PH subtypes, the enzyme deficiency leads to endogenous overproduction of the metabolic end-product oxalate, which is almost exclusively eliminated by the kidneys.[1,2] Chronic hyperoxaluria places patients at risk for kidney deposition of calcium oxalate as stones (nephrolithiasis) and/or as crystals in the parenchyma (nephrocalcinosis), which often results in progressive kidney damage or kidney failure.[1,2,4–10] Patients with PH1 can present early in childhood, often with end-stage kidney failure.[5] As kidney function declines, a marked increase in plasma oxalate (Pox) can lead to calcium oxalate deposition in extrahepatic tissues in a process called systemic oxalosis.[1,2,10–13] This

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devastating complication commonly affecting the bones, retina, blood vessels, myocardium, and skin is associated with high morbidity and mortality.[1,2,11]

For years, only supportive therapies were available for the management of PH, with liver transplantation being the only potential curative option to correct the underlying metabolic deficiency.[14–26] In 2020, the treatment landscape for PH1 was altered dramatically by the availability of the ribonucleic acid interference (RNAi) therapeutic lumasiran (Alnylam Pharmaceuticals).[27] Hepatic glycolate oxidase is one of the enzymes[28] responsible for production of the oxalate precursor glyoxylate;[27] lumasiran reduces oxalate production by depleting hepatic glycolate oxidase, which results in an increase of plasma glycolate levels.[27,28]

Nedosiran is an investigational RNAi therapy designed to treat PH via targeted inhibition of hepatic lactate dehydrogenase (LDH) expression (encoded by the *LDHA* gene).[29] Animal data and data from the phase 1 PHYOX1 study indicate that hepatic LDH is a viable therapeutic target for both PH1 and PH2, showing no evidence of off-target effects, such as in skeletal muscles.[29–32] In PHYOX1, single-dose nedosiran administered to participants with PH1 or PH2 led to a fall in urinary oxalate (Uox) excretion consistent with its putative mechanism of action; no serious safety issues were identified.[29,30]

Thus, a pivotal, randomized controlled study (PHYOX2) was conducted to assess the efficacy and safety of nedosiran versus placebo in participants with PH1 or PH2.

METHODS

Study design and conduct

PHYOX2 was a multinational, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of monthly subcutaneous nedosiran in participants with PH1 or PH2 over a 6-month treatment period (ClinicalTrials.gov number: NCT03847909; EudraCT number: 2018-003098-91; Figure 1). The study was conducted between October 2019 and June 2021, in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines of the International Conference on Harmonization, and all applicable laws and regulations. Written informed consent was obtained from all adult participants and the parents or legal guardians of participating children; children assented as appropriate. An independent data and safety monitoring committee provided a periodic review of the efficacy and safety data. Full details of the methodology are provided in the Supplementary Supplementary Material (Supplementary Methods, Supplementary Table S1 and S2).

Study population and treatment

Male or female participants ≥6 years old with genetically confirmed PH1 or PH2 who had a 24-hour Uox excretion ≥0.7 mmol (per 1.73 m^2 body surface area [BSA] in age <18 years) and an estimated glomerular filtration rate (eGFR) ≥30 ml/min per 1.73 m^2 BSA were eligible. At least 12 of the enrolled participants were required to have at least one 24-hour Uox excretion ≥1.6 mmol (adjusted per 1.73 m^2 BSA in participants <18 years old). Key exclusion criteria included prior kidney or liver transplantation, planned transplantation during the trial period, current or planned dialysis during the trial period, and use of an RNAi drug within the last 6 months.

All participants were randomly assigned 2:1 to receive nedosiran or placebo once monthly for 6 months (on days 1, 30, 60, 90, 120, and 150), with both interventions administered as subcutaneous injections into the abdomen or thigh. Nedosiran was administered as the sodium salt, 170 mg, which corresponds to 160 mg of free acid. The dose of nedosiran sodium by age group and weight is indicated in Figure 1. Placebo was 0.9% saline for injection administered at a volume to match that of the active intervention. An adaptive randomization via minimization method was used to allocate participants to treatment arms with respect to age (6–11, 12–17, and ≥18 years) and eGFR (<45 and ≥45 ml/min per 1.73 m^2).

All participants were instructed to continue after their standard of care measures for PH. As vitamin C and diet can affect Uox excretion in patients with PH,[33] all participants were specifically instructed to refrain from taking vitamin C supplements, including multivitamins, and to avoid oxalate-rich foods at all times during the study.

Assessments and endpoints

Twenty-four-hour urine samples were collected during the screening period and on days 30, 60, 90, 120, 150, and at day 180 (end of the study). Participants were required to have <20% variation in 24-hour urinary creatinine excretion (mmol/24 h/kg) on values derived from two 24-hour urine collections in the screening period. If the initial pair of screening values did not meet this criterion, participants were given the opportunity to perform a second pair of collections. On-treatment 24-hour urinary creatinine excretion values were required to be within 20% of baseline, defined as the mean of the 2 screening values; collections that did not meet this criterion were repeated. Collections with a reported duration of <22 hours or >26 hours at screening or on treatment were considered invalid, and participants were asked to repeat them.

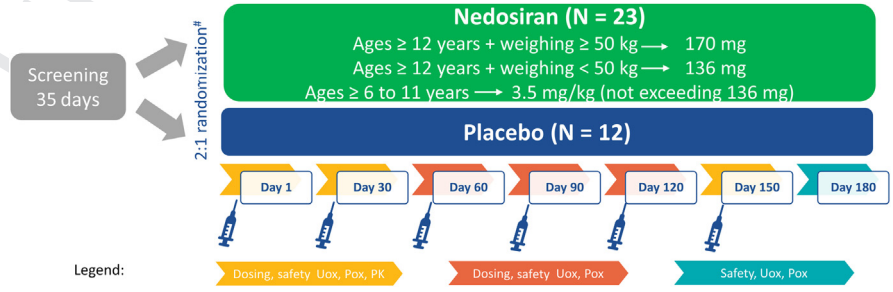


Figure 1 | PHYOX2 study design. #An adaptive randomization via the minimization method was used to allocate participants to treatment arms with respect to age and estimated glomerular filtration rate. PK, pharmacokinetics; Pox, plasma oxalate; Uox, urinary oxalate.

The primary endpoint in the United States, as recommended by the Food and Drug Administration, was the percent change from baseline in 24-hour Uox excretion, as assessed by area under the curve (AUC) from day 90 to day 180. This measure was proposed to assess a reduction in oxalate burden over time rather than at a single time point at the end of the study. The observed percent change in 24-hour Uox excretion from baseline between day 90 and day 180 was used to calculate a standardized AUC for each individual participant, which signifies the integrated Uox excretion over the 90-day period. A positive AUC 24-hour Uox value represents an improvement in the participants' condition (i.e., a reduction in 24-hour Uox from baseline). Twenty-four-hour Uox excretion was adjusted for BSA in participants aged <18 years to normalize age-related variation in oxalate excretion.[34] Because of the differences in primary endpoint analyses recommended by the European Medicines Agency, the primary endpoint outside of the United States was the proportion of participants with a ≥70% Uox reduction based on AUC and/or normal (i.e., <0.46 mmol per 24 hours; upper limit of assay-normal [ULN]) or near-normal (i.e., ≥0.46 to <0.60 mmol per 24 hours; ≥ULN to <1.3 × ULN) 24-hour Uox excretion on at least 2 consecutive visits, starting at day 90.

Prespecified secondary efficacy endpoints in order of hierarchical statistical testing were: (i) the proportion of participants reaching normal or near-normal 24-hour Uox excretion on at least 2 consecutive visits, starting at day 90 (key secondary endpoint); (ii) percent change in Pox from baseline to day 180; (iii) percent change in the number and summed surface area of kidney stones identified via kidney ultrasound from baseline to day 180; and (iv) rate of change in eGFR from baseline to day 180. Exploratory efficacy endpoints included the number of stone events over the 6-month period, AUC of 24-hour Uox-to-creatinine ratio from day 90 to day 180, and quality of life (36-Item Short Form Survey and EuroQol-5-dimensions-5-levels in adults; Pediatric Quality of Life Inventory in children).

Safety was assessed via adverse event (AE) reporting along with physical examinations, electrocardiograms, vital signs, and clinical laboratory tests conducted at screening and throughout the study.

Analysis populations

The primary endpoint was analyzed in the modified intent-to-treat (ITT) population, defined as all participants who were randomized and had at least 1 postbaseline efficacy assessment after the day 90 dosing visit. Secondary and tertiary efficacy analyses were performed either in the modified ITT population or ITT population (defined as all participants who were randomized and had at least 1 postbaseline efficacy assessment). The safety population included all participants randomly assigned to study intervention who took at least 1 partial or full dose of study intervention.

Statistics

A planned enrollment of 36 participants was estimated to yield approximately 94% power to detect a 40% difference (nedosiran minus placebo) in AUC Uox over 90 days (days 90–180) at a 1-sided superiority level of 0.025. The treatment comparison for AUC was based on an analysis of covariance model, with the treatment group as a main effect and baseline 24-hour Uox excretion, age category (6–11, 12–17, and ≥18 years), and eGFR category (<45 ml/min per 1.73 m^2 and eGFR ≥45 ml/min per 1.73 m^2) as covariates. Multiple imputation under the missing at random approach was used to impute missing values and those values not meeting the stringent urine collection completeness criteria. Eight prespecified and 1 *post hoc* sensitivity analyses were performed for the primary efficacy endpoint, and 1 prespecified sensitivity analysis was performed on the key secondary endpoint (Supplementary Table S1). Prespecified subgroups for analysis of the primary endpoint included participants with at least 1 baseline 24-hour Uox ≥1.6 mmol (adjusted per 1.73 m^2 BSA in participants aged <18 years) and other subgroups (data permitting) based on PH type, age, eGFR, and gender.

A hierarchical testing procedure for the prespecified primary and secondary efficacy endpoints was implemented to control the overall type I error rate. *P* values generated in subsequent *post hoc* analysis should be considered nominal.

Analysis of the primary endpoint in the PH1 subgroup was prespecified. Pox dynamics in the PH1 and PH2 subgroups and the percent change in the summed surface area and number of kidney stones from baseline to day 180 in the PH1 subgroup were analyzed *post hoc*.

RESULTS

Study population

Of the 57 participants screened, 35 participants across 11 countries were considered eligible and randomly assigned in a 2:1 ratio to receive nedosiran (n = 23) or placebo (n = 12; Supplementary Figure S1). Thirty-three of the 35 participants (94%) completed study treatment and continued onto the open-label extension study (PHYOX3; NCT04042402). One participant each from the nedosiran and placebo arms discontinued study treatment early and withdrew from the study (see the section on Safety for details).

Participants were genetically diagnosed with PH1 (n = 29) or PH2 (n = 6). Baseline demographic and disease characteristics were generally balanced between the 2 treatment arms, with the exception of 24-hour Uox excretion at baseline, which was higher in the placebo arm (Table 1). A higher proportion of placebo participants (83%) than nedosiran participants (30%) had a 24-hour Uox excretion ≥1.6 mmol (baseline 24-hour Uox excretion was not a stratification factor for participant randomization to treatment arms). Pox was well balanced between the treatment arms. Pyridoxine was received by 12 of 23 participants (52.2%) in the nedosiran group and by 9 of 12 participants (75.0%) in the placebo group.

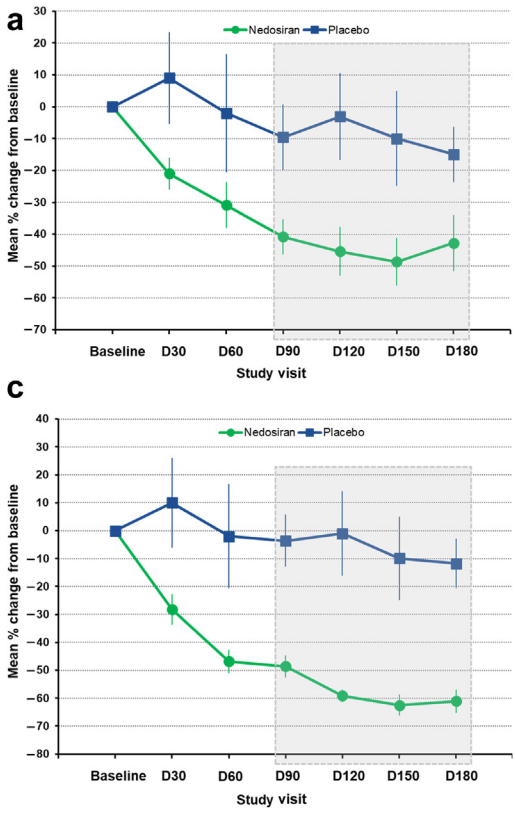
Efficacy

Urinary oxalate. PHYOX2 achieved the primary endpoint with a statistically significantly greater reduction in Uox, as measured by the AUC from day 90 to day 180 in the nedosiran arm versus the placebo arm (least-squares [LS] mean [standard error]: +3507.4 [788.49] vs. −1664.4 [1189.96]; LS difference [nedosiran minus placebo] 5171.7; 95% CI: 2929.3–7414.2; $P < 0.001$; Figure 2a and b). At day 180, participants treated with nedosiran had a mean (SD) Uox of 0.68 (0.39) mmol/24 h (change from baseline, −0.61 [0.54]) compared with 1.70 (1.07) mmol/24 h (change from baseline, −0.27 [0.58]) in the placebo group. The LS mean difference (nedosiran minus placebo) in reduction in Uox from baseline was 51% in the nedosiran arm, when averaged over day 90 to day 180 ($P < 0.001$; *post hoc* analysis;

Table 1 | Baseline demographic and clinical characteristics (safety population)

Characteristic	Nedosiran (N = 23)	Placebo (N = 12)
Age, yr		
Mean (SD)	23.7 (11.95)	23.6 (11.48)
Median (range)	20.0 (9–46)	20.5 (10–41)
Age category, yr, n (%)		
6–11	3 (13.0)	2 (16.7)
12–17	6 (26.1)	4 (33.3)
≥18	14 (60.9)	6 (50.0)
Female, n (%)	12 (52.2)	6 (50.0)
Race, n (%)		
White	15 (65.2)	10 (83.3)
Asian	6 (26.1)	0
Multiple	0	1 (8.3)
Missing	2 (8.7)	1 (8.3)
Ethnicity, n (%)		
Not Hispanic or Latino	19 (82.6)	11 (91.7)
Hispanic or Latino	2 (8.7)	0
Missing	2 (8.7)	1 (8.3)
Weight, kg		
Mean (SD)	64.9 (19.3)	72.8 (27.3)
Median (range)	64.2 (31.8–115.9)	65.4 (42.7–127.0)
Body mass index, kg/m^2		
Mean (SD)	23.2 (5.1)	26.0 (6.3)
Median (range)	23.2 (14.0–34.8)	24.1 (18.3–37.4)
PH type, n (%)		
Type 1	18 (78.3)	11 (91.7)
Type 2	5 (21.7)	1 (8.3)
Years since PH diagnosis, mean (SD)	7.1 (6.9)	7.4 (8.8)
Vitamin B6 use, n (%)	12 (52.2)	9 (75.0)
Baseline 24-h Uox,[a] mmol/d		
Mean (SD)	1.33 (0.47)	1.96 (0.71)
Median (range)	1.28 (0.71–2.60)	1.79 (1.15–3.68)
High baseline Uox, n (%)[b]	7 (30.4)	10 (83.3)
eGFR, ml/min per 1.73 m^2 [c]		
Mean (SD)	89.5 (37.5)	82.0 (30.0)
Median (range)	86.0 (35–197)	77.0 (44 131)
IQR	72.0, 110.0	56.5, 109.5
eGFR category, n (%)		
<45 ml/min per 1.73 m^2	4 (17.4)	1 (8.3)
≥45 ml/min per 1.73 m^2	19 (82.6)	11 (91.7)
Chronic kidney disease stage, n (%)		
Stage 1	12 (52.2)	5 (41.7)
Stage 2	8 (34.8)	2 (16.7)
Stage 3A	0	2 (16.7)
Stage 3B	3 (13.0)	2 (16.7)
Missing	0	1 (8.3)
Baseline plasma oxalate, μmol/l		
Mean (SD)	7.9 (5.11)	8.8 (5.06)
Median (range)	6.0 (2–21)	9.0 (2–18)
Any kidney stone event in last 12 mo, n (%)	8 (34.8)	6 (50.0)
Number of kidney stone events in last 12 mo, n	8	6
Mean (SD)	1.4 (0.74)	1.0 (0.00)
Median (range)	1 (1–3)	1 (1–1)
Baseline number of kidney stones, n	17	11
Mean (SD)	2.9 (2.4)	6.5 (9.6)
Median (range)	2 (1–9)	3 (1–34)
Baseline kidney stone summed surface area, mm^2, n	17	11
Mean (SD)	176.5 (302.2)	140.6 (142.8)
Median (range)	78.0 (21–1241)	71.0 (2–461)

BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PH, primary hyperoxaluria.
Baseline 24-hour Uox is calculated as the average of the last 2 screening results before the first dose of study intervention. BSA-adjusted 24-hour Uox values (mmol/24 h per 1.73 m^2) are used for participants <18 years old; eGFR <45 ml/min per 1.73 m^2 included CKD stage 3B and eGFR ≥45 ml/min per 1.73 m^2 included CKD stages 1, 2, and 3A.
[a]BSA adjusted 24-hour Uox values were used for participants <18 years. BSA-adjusted 24-hour Uox = 24-hour Uox value × (1.73/BSA of participant).
[b]Participants were identified as having a high baseline 24-hour Uox value if at least 1 of the last 2 screening results before the first dose of study intervention was ≥1.6 mmol per 24 hours.
[c]The eGFR was based on eGFR CKD Epidemiology Collaboration equation in adult participants (≥18 years old)[35] and the Schwartz *et al.*[36] 2012 multivariate equation in pediatric participants (6–17 years old). In Japan, the eGFR was calculated using a Japanese specific equation based on creatinine.
The safety population includes all participants randomly assigned to study intervention and who took at least 1 partial or full dose of study intervention. Participants were analyzed according to the intervention they actually received.



b

Standardized AUC 24-h Uox from day 90 to day 180	Nedosiran (N = 22)	Placebo (N = 12)
LS mean (SE)	3507.4 (788.49)	−1664.4 (1189.96)
95% CI for LS mean	1961.7, 5053.1	−3397.2, 668.4
LS mean differences from placebo (SE)	5171.7 (1144.07)	
95% CI for difference from placebo	2929.3, 7414.2	
P value for difference from placebo	<0.001	

d

Standardized AUC 24-h Uox from day 90 to day 180	Nedosiran (N = 17)	Placebo (N = 11)
LS mean (SE)	4575.1 (905.37)	−1316.7 (1284.81)
95% CI for LS mean	2799.9, 6350.3	−3835.6, 1202.2
LS mean differences from placebo (SE)	5891.8 (1126.99)	
95% CI for difference from placebo	3682.8, 8100.7	
P value for difference from placebo	<0.001	

Figure 2 | Standardized area under the curve (AUC) 24-hour urinary oxalate (Uox) from day 90 to day 180 (modified intent to treat [mITT] population [all participants in the ITT population who had at least 1 efficacy assessment after the day 90 dosing visit]) after monthly administration of nedosiran or placebo. Panels (**a**) and (**c**) show the percent change in Uox from baseline in the overall mITT population (**a**) and the PH1 mITT population (**c**) based on observed (unadjusted) Uox values, respectively. The gray box around day 90 to day 180 represents schematically the data (% change in Uox from baseline) used to compute the standardized AUC (panels **b** and **d**), wherein estimates for LS means, 95% confidence intervals (CIs), and *P* values are from an analysis of covariance model with the treatment arm as the main effect and baseline 24-hour Uox value, age category (6–11, 12–17, and ≥18 years), and estimated glomerular filtration rate (eGFR) category (eGFR <45 ml/min per 1.73 m^2, eGFR ≥45 ml/min per 1.73 m^2) as covariates for adjustment. Multiple imputation under the missing at random approach was used to replace missing values and those values not meeting completeness criteria (repeated values that are not within 20% of baseline and collections with a duration of <22 hours or greater than 26 hours). Standardized AUC = (AUC / actual days from day 90 visit to day 180) × 90. Error bars represent ± SEM; baseline 24-hour Uox was calculated as the average of the last 2 screening results before the first dose of study intervention. Body surface area–adjusted 24-hour Uox values used for participants <18 years. LS, least squares.

Supplementary Figure S2, left graph). The efficacy of nedosiran to lower Uox from day 90 to day 180 was confirmed in all prespecified sensitivity analyses (Supplementary Table S3). Of note, the primary endpoint analysis was performed (as described above) with baseline 24-hour Uox as a covariate. The primary endpoint was also analyzed in the subgroup of participants with at least 1 baseline Uox ≥1.6 mmol/24 h. Nedosiran was associated with a statistically significant reduction in Uox AUC versus placebo (LS mean: 3940.2 vs. 1046.3, $P = 0.019$) in this subgroup as well. These data were corroborated by *post hoc* sensitivity analyses performed by excluding participants with baseline Uox excretion >2.8 mmol/24 h, which demonstrated that the imbalance in baseline Uox did not influence the Uox reduction observed with nedosiran (Supplementary Table S4).

A statistically significantly greater proportion of participants in the nedosiran arm than the placebo arm (50% vs. 0%; $P = 0.002$) achieved the key secondary endpoint of normal or near-normal 24-hour Uox on at least 2 consecutive visits, starting at day 90 (Table 2). This result was supported by a sensitivity analysis using BSA-adjusted Uox values for all participants (Supplementary Table S3). A significantly greater proportion of participants in the nedosiran arm than the placebo arm achieved a ≥70% Uox reduction based on AUC and/or normal or near-normal 24-hour Uox excretion on at least 2 consecutive visits (59% vs. 0%; $P < 0.001$; Table 2). Sixteen of 22 participants (73%) in the nedosiran arm achieved normal (n = 13) or near-normal (n = 3) 24-hour Uox excretion at least once during treatment in the trial versus 1 participant in the placebo arm (8%).

The sustained Uox reduction was primarily seen in the nedosiran-treated participants with PH1 (Table 2; Figure 2c and d). Nedosiran-treated participants in the PH1 subgroup achieved statistically significant differences from placebo for the primary endpoint ($P < 0.001$; based on prespecified subgroup analysis) and key secondary endpoint ($P < 0.001$;

Table 2 | Normalization or near-normalization of 24-hour Uox excretion[a,b] starting at day 90 in the overall study population and in the PH1 subgroup (mITT population)

Parameter	Nedosiran (N = 22)		Placebo (N = 12)
Normalization or near-normalization of 24-hour Uox excretion on ≥2 consecutive visits, % (overall population)	50		0
P value		0.002	
≥70% reduction in 24-hour Uox based on AUC and/or normalization or near-normalization of 24-hour Uox excretion on ≥2 consecutive visits,[c] % (overall population)	59		0
P value		<0.001	
	Nedosiran (N = 17)		**Placebo (N = 11)**
Normalization or near-normalization of 24-hour Uox excretion on ≥2 consecutive visits, % (PH1 subgroup)	64.7		0
P value		<0.001	

AUC, area under the curve; mITT population, modified intent-to-treat (all participants in the ITT population who have at least 1 efficacy assessment after the day 90 dosing visit); PH, primary hyperoxaluria; ULN, upper limit of the normal range; Uox, urinary oxalate.
[a]24-hour Uox excretion is considered normal if the value is <0.46 mmol per 24 hours (ULN), and near-normal if the value is ≥0.46 to <0.6 mmol per 24 hours. Thus, the term normal or near-normal 24-hour Uox excretion is defined as <1.3 × ULN (i.e., Uox <0.6 mmol per 24 hours).
[b]Body surface area–adjusted 24-hour urinary oxalate values are used for participants <18 years.
[c]Primary study endpoint outside of the United States.

based on *post hoc* subgroup analysis). Nedosiran-treated participants with PH1 had a 59% LS difference (nedosiran minus placebo) in mean reduction in Uox from baseline between day 90 and day 180 ($P < 0.001$; Supplementary Figure S2, right graph) and a higher mean maximum reduction in Uox from baseline (68%) at any point during the study compared with placebo (31%; $P < 0.001$). Among PH1 participants, and in contrast to the placebo arm, the nedosiran arm had a steady and sustained decrease in mean 24-hour Uox excretion, beginning at the first visit (day 30) and entering the near-normal range by day 120 (Figure 3). At day 180, the mean [SD] Uox of nedosiran-treated PH1 participants remained in the near-normal range (0.52 [0.27] mmol/24 h; change from baseline = −0.83 [0.36] mmol/24 h); in contrast, the placebo-treated PH1 participants remained hyperoxaluric (1.78 [1.10] mmol/24 h; change from baseline = −0.21 [0.57] mmol/24 h). There was no consistent pattern observed for 24-hour Uox excretion in treated or untreated PH2 participants (Figure 4).

Exploratory analysis of the overall ITT population revealed that nedosiran was associated with statistically significant Uox reductions versus placebo, based on LS mean AUC 24-hour Uox from baseline to day 180 (5083.4 vs. −2503.1, respectively; LS mean difference from placebo, 7586.6; $P < 0.001$). The LS mean AUC Uox-to-creatinine ratio in the modified ITT population from day 90 to day 180 also indicated a significant reduction in Uox compared with placebo (3351.2 vs. −1860.4, respectively; LS mean difference from placebo, 5211.6; $P < 0.001$).

Plasma oxalate. Among participating adults in the ITT population (17 with PH1; 2 with PH2), the prespecified Pox treatment comparison revealed a trend toward a greater reduction in the nedosiran arm (median 25% reduction from 8.0 μmol/l at baseline to 6.5 μmol/l at day 180) versus no change in the placebo arm (median Pox 9.0 μmol/l at baseline to 8.0 μmol/l at day 180; 1-sided $P = 0.026$ for nedosiran vs. placebo; Figure 5). Among adults with PH1, *post hoc* analysis indicated that Pox declined in the nedosiran arm (median Pox 8.0 μmol/l at baseline to 6.0 μmol/l at day 180) and increased in the placebo arm (median Pox 8.0 μmol/l at baseline to 8.5 μmol/l at day 180), resulting in a statistically significant between-treatment difference ($P = 0.017$; Figure 5).

Among nedosiran-treated adults (PH1 or PH2), there was a greater reduction in Pox at day 180 in the subgroup of participants (n = 4) with baseline eGFR <45 ml/min per 1.73 m^2, compared with the reduction observed in the subgroup with higher eGFR (Supplementary Figure S3).

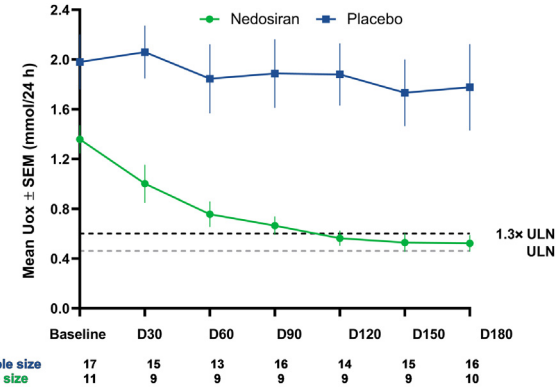


Figure 3 | Mean absolute change in 24-hour urinary oxalate (Uox) excretion for PH1 participants (modified intent to treat [mITT] population [all participants in the ITT population who had at least 1 efficacy assessment after the day 90 dosing visit]). Baseline 24-hour Uox was calculated as the average of the last 2 screening results before the first dose of study intervention. Uox adjusted for body surface area (BSA) for participants age <18 years. The gray dotted line depicts the upper limit of the normal range (ULN), and the black dotted line depicts 1.3 times ULN.

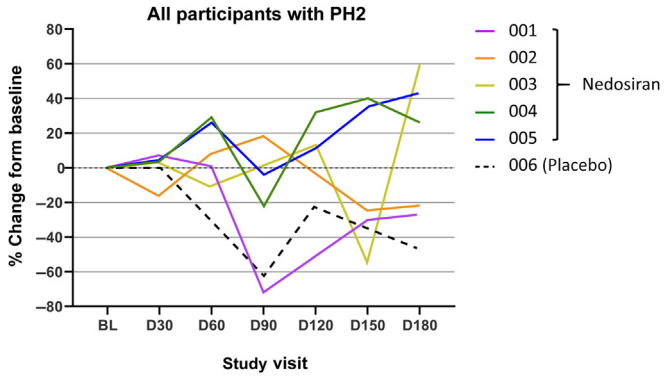


Figure 4 | Individual percent change in 24-hour urinary oxalate (Uox) excretion in participants with PH2. Baseline (BL) 24-hour Uox was calculated as the average of the last 2 screening results before the first dose of study intervention. Only data from complete collections are shown (D120 data for participants 001 and 002 were missing). body surface area–adjusted 24-hour Uox values used for participants aged <18 years.

Stone burden and kidney function. *Post hoc* analysis revealed that nedosiran treatment versus placebo was associated with a significant reduction in the summed surface area of kidney stones at day 180 among PH1 participants but not in the overall ITT population (Table 3). No differences were observed between the nedosiran and placebo arms regarding the percent change from baseline to day 180 in the number of kidney stones ($P = 0.46$) in the ITT population. The annualized stone event rate in the ITT population was significantly lower in the nedosiran arm than the placebo arm (0.43 vs. 1.51, $P = 0.006$). No significant within- or between-treatment changes from baseline to day 180 were detected regarding rate of change in eGFR in the ITT population.

Quality of life. No significant within- or between-treatment changes from baseline to day 180 were detected in 36-Item Short Form Survey, EuroQol-5-dimensions-5-levels, or Pediatric Quality of Life Inventory measures in the ITT population.

Safety

The extent of exposure to assigned intervention was similar in each treatment group in terms of both mean number of study drug administrations for a participant (5.6 in the nedosiran arm and 5.9 in the placebo arm) and mean duration of treatment (4.75 months in the nedosiran arm and 4.82 months in the placebo arm), acknowledging that the span between first dose and last dose is not representative of total exposure.

Nineteen participants (83%) in the nedosiran arm and 10 participants (83%) in the placebo arm had at least 1 treatment-emergent AE (Table 4). Most AEs were mild or moderate in severity. A greater proportion of participants in the nedosiran than placebo arm had a treatment-related AE (44% vs. 25%); the most common treatment-related AE in the nedosiran arm was injection site erythema (22%; Supplementary Table S5).

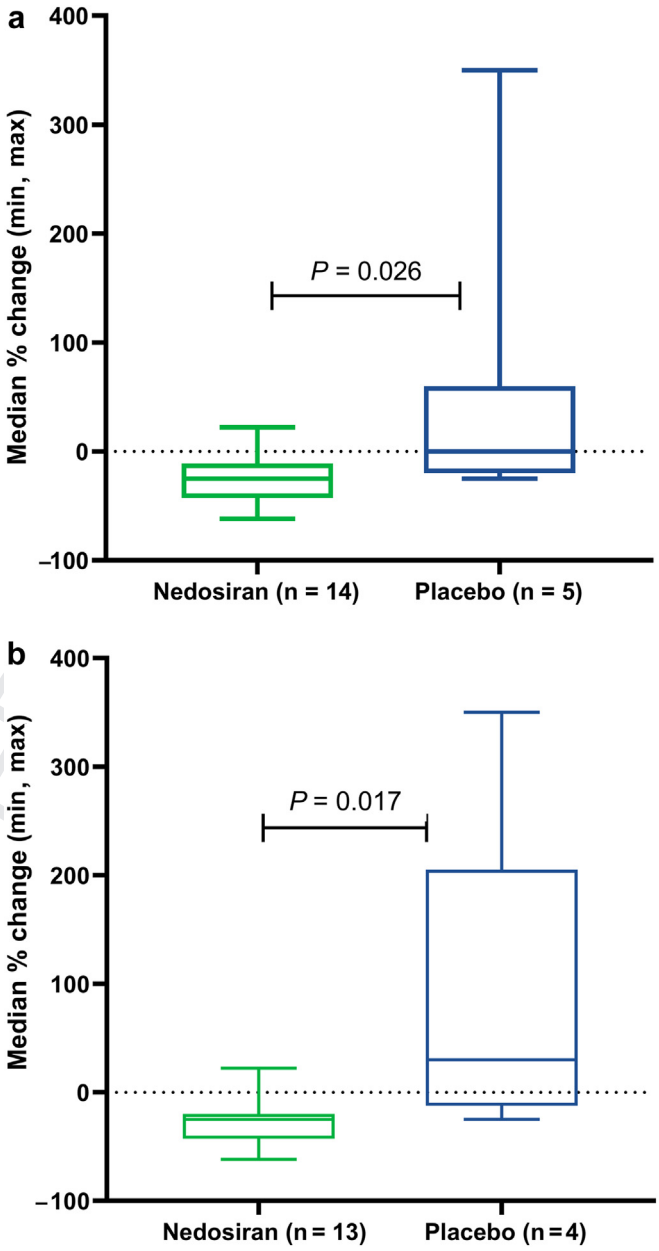


Figure 5 | Percent change in plasma oxalate from baseline to day 180 among adult participants (intent-to-treat [ITT] population [all participants who were randomized and had at least 1 postbaseline efficacy assessment]).[a] Panel (**a**) depicts adult participants with PH1 or PH2 and panel (**b**) depicts adult participants with PH1 only. In panel (**a**), baseline mean (SD) plasma oxalate (μmol/l): nedosiran arm, 9.4 (5.4); placebo arm, 7.7 (3.5). In panel (**b**), baseline mean (SD) plasma oxalate (μmol/l): nedosiran arm, 7.9 (5.1); placebo arm, 8.8 (5.1). [a]All participants who were randomized and had ≥1 postbaseline efficacy assessment. The boxes extend from the lower quartile (Q1) to upper quartile (Q3); the error bars represent the lowest and highest values. Postscreening plasma oxalate sampling was conducted only in adults (≥18 years old); missing values at day 180 are not imputed; *P* value from a 1-sided Wilcoxon rank-sum test.

Injection-site reactions occurred in 2 of 23 nedosiran-treated participants (9%) and in none of the placebo-treated participants. All injection-site reactions were graded as Common Terminology Criteria for Adverse Events grade 1

Table 3 | Percent change in summed surface area of kidney stones (mm^2) in the overall study population and the PH1 subgroup (ITT populations) over the 6-month treatment period

Parameter	Overall study population		PH1 only	
	Nedosiran (N = 17)	Placebo (N = 11)	Nedosiran (N = 13)	Placebo (N = 10)
Median (min, max) at baseline	78.0 (21, 1241)	71.0 (2, 461)	78.0 (21, 494)	69.0 (2, 296)
Median (min, max) at day 180	44.0 (0, 1846)	116.0 (28, 636)	30.5 (0, 473)	100.0 (28, 277)
Median % change from baseline to day 180	−2.1	+21.8	−17.9	+5.6
P value	0.083 (not significant)		0.024[a]	

ITT, intent-to-treat; PH, primary hyperoxaluria.
ITT population includes all participants who were randomized and had at least 1 postbaseline efficacy assessment.
[a]Nominal statistical significance.

and resolved by the end of trial (range of duration, 2–50 days). No participants in either group experienced muscle pain or weakness.

One serious AE occurred in a nedosiran-treated participant, and 3 serious AEs occurred in 2 placebo-treated participants. The serious AE in the nedosiran-treated participant was a severe fluctuating tachycardia of undetermined origin considered by the investigator as possibly related to nedosiran due to the temporal relationship of event to study drug exposure; this led to study withdrawal. An expert review by 2 independent external cardiac electrophysiologists suggested that the tachycardia observed in a follow-up Holter examination and presumed to be same as that having produced the symptoms at the time of the AE was supraventricular in origin, did not pose a significant risk, and was unlikely to be related to nedosiran. Although we cannot definitively rule out the role of nedosiran in this AE, continued pharmacovigilance during clinical development will aid the detection of any trends related to this AE.

No clinically important changes in laboratory or other clinical parameters, physical examinations, or electrocardiograms were observed in association with nedosiran. There were no clinically significant trends in creatine kinase elevations in either the nedosiran or placebo arm. No participants in the nedosiran arm had treatment-emergent antidrug antibodies.

DISCUSSION

Twenty-four-hour Uox excretion is an accepted surrogate marker of PH disease burden and long-term risk for kidney failure.[37,38] In PHYOX2, we collected monthly 24-hour Uox excretion data and calculated the AUC of 24-hour Uox change from baseline between day 90 and day 180. This endpoint is a metric that provides insights into the consistency and durability of Uox reduction over time rather than assessing Uox reduction at a single time point at the end of the study. PHYOX2 participants who received subcutaneous nedosiran had a statistically and clinically significant and sustained reduction in Uox compared with placebo. The efficacy of nedosiran withstood multiple prespecified sensitivity analyses, and nedosiran was equally efficacious in the subgroup of participants with at least 1 baseline Uox ≥1.6 mmol/24 h. In addition, a significantly greater proportion of nedosiran-treated than placebo-treated participants achieved normal or near-normal (<1.3 × ULN) Uox excretion. The trial criteria regarding individual 24-hour Uox excretion measurements, the frequency of urine collections, and fulfillment of prespecified efficacy outcomes were all stringent, giving a high degree of confidence in the results.

Nedosiran efficacy in PHYOX2 was driven by substantial lowering of Uox excretion in participants with PH1,

Table 4 | TEAEs in participants with primary hyperoxaluria type 1 or 2 who received nedosiran or placebo (safety population)

TEAE	Nedosiran (N = 23)	Placebo (N = 12)
	Number (%) of participants, number of events	
Any	19 (83), 101	10 (83), 54
Treatment related	10 (44), 36	3 (25), 12
Leading to treatment discontinuation	1 (4), 1	1 (8), 1
Serious	1 (4), 1	2 (17), 3
Serious and treatment related	1 (4), 1	0
Severe	1 (4), 1	4 (33), 7
Fatal	0	0
Occurring in ≥10% of participants[a]		
Injection site erythema	5 (22), 11	0
Headache	4 (17), 6	3 (25), 3
Nausea	4 (17), 4	1 (8), 1
Abdominal cramp[b]	3 (13), 3	2 (17), 2
Nephrolithiasis[c]	2 (9), 3	3 (25), 8
Fatigue	1 (4), 2	2 (17), 2
Renal colic[d]	1 (4), 1	2 (17), 3 Q20
Back pain	0	2 (17), 2
Of special interest	5 (22), 19	5 (42), 13
Injection-site reaction[e]	2 (9), 11	0
Kidney stone events[f]	3 (13), 8	5 (42), 13
Muscle pain or weakness	0	0

TEAE, treatment-emergent adverse event.
[a]In either group.
[b]Includes the terms abdominal pain, abdominal discomfort, and upper abdominal pain.
[c]Renal stones requiring medical intervention or stone passage with or without hematuria.
[d]Renal colic requiring medication.
[e]Injection-site reactions were defined as signs or symptoms at the injection site with a time to onset of 4 or more hours from the time of study intervention administration.
[f]Combined total of both nephrolithiasis and renal colic events.
The safety population includes all participants randomly assigned to study intervention and who took at least 1 partial or full dose of study intervention.

with mean 24-hour Uox excretion sustained in the normal or near-normal range in this subgroup. In contrast, there was no consistent pattern of change in 24-hour Uox excretion in the PH2 subgroup. We note that the 1 participant with PH2 who received placebo had a 40% reduction in 24-hour Uox excretion, which reflects high intraindividual variation in this parameter without an obvious explanation. A reduction in Uox excretion was expected in the nedosiran-treated PH2 subgroup based on the mode of action of this RNAi, pharmacodynamic data from PHYOX1, and animal studies.[29,31,32] Several factors could conceivably account for these inconclusive results in PH2 participants, including the small sample size (n = 6), the dose employed being insufficient to produce an effect, extrahepatic production of oxalate,[39] and additional and unknown oxalate synthetic pathways in the liver not dependent on LDH activity. LDH inhibition in patients with PH2 could be analyzed by L-glycerate measurements and stable isotope fusion methods. These hypotheses and further long-term follow-up of PH2 participants are under active investigation.

In nedosiran-treated PH1 participants, a reduction in Uox excretion was accompanied by improvements in Pox and stone burden (number and summed surface area of kidney stones), and kidney function was preserved. The reduction in Pox in the nedosiran arm versus the placebo arm was modest possibly because normal Pox levels in both arms at baseline meant that the margin for improvement was small (i.e., a floor effect). Although it is encouraging that nedosiran is associated with favorable trends in other clinical manifestations beyond Uox, these results were based on subgroup analyses and need confirmation with long-term follow-up data.

Nedosiran was generally safe and well tolerated in all subgroups. The AE profile of nedosiran was consistent with previously reported clinical data on nedosiran,[29] and no new safety risks were identified. The most frequent treatment-related AEs were injection-site reactions, which are a common occurrence with the administration of many subcutaneous RNAi therapeutics. Two nedosiran-treated participants experienced 11 injection-site reactions in PHYOX2, which represented 8% of the total 146 injections in this study. Importantly, all injection-site reactions were mild and resolved by the end of the study. The absence of muscle pain or weakness in conjunction with elevated creatine kinase with nedosiran suggests that the nedosiran-mediated inhibition of hepatic LDH does not appear to elicit any off-target effects in the skeletal muscle.

Acknowledging the lack of head-to-head clinical trial data, we postulate based on data from this 6-month study that nedosiran may be similarly effective to lumasiran for reducing 24-hour Uox excretion in the population studied; the placebo-adjusted LS mean reduction in 24-hour Uox excretion from baseline to month 6 was 54% with lumasiran and 59% with nedosiran (based on the mean percent change across months 3–6).[27] More studies are required to detect any long-term differences between nedosiran and lumasiran regarding sustained effects on Uox and Pox, and the clinical endpoints of stone burden and kidney function that may be associated with specific attributes of these RNAi therapeutics (including dosing regimen). Nevertheless, it is valuable for clinicians and patients to have an additional, effective treatment option, given the unknown potential for interindividual variability in the extent of treatment response to either lumasiran or nedosiran.

PHYOX2 was limited by trial brevity and exclusion of participants <6 years of age or with kidney failure. These questions are being addressed by the ongoing long-term open-label studies PHYOX3 (NCT04042402), PHYOX7 (NCT04580420), and PHYOX8 (NCT05001269). In PHYOX2, the placebo arm had higher mean 24-hour Uox excretion at baseline than the nedosiran arm, and randomization was not stratified by Uox excretion. However, prespecified subgroup analysis of participants in the nedosiran and placebo arms with 24-hour Uox excretion ≥1.6 mmol at baseline revealed a marked reduction in Uox AUC from day 90 to day 180 in the nedosiran arm versus the placebo arm. A *post hoc* sensitivity analysis using an analysis of covariance model that excluded the 2 placebo-treated participants with the highest 24-hour Uox excretion at baseline also showed highly comparable results to the primary efficacy analysis, suggesting that the treatment effect was not influenced by baseline Uox excretion.

In conclusion, this pivotal, randomized, placebo-controlled trial demonstrated that monthly subcutaneous doses of nedosiran were safe and well tolerated in all treated subgroups. Nedosiran induced marked reductions in Uox excretion in PH1 participants, with the 24-hour Uox dropping to and persisting in the normal or near-normal range in most participants. Nedosiran efficacy data in the PH2 subgroup were inconclusive, suggesting that further study is warranted to elucidate the physiology in this population for which no curative options exist.

DISCLOSURE

MAB is a consultant for, has received honoraria from, and is on the advisory board of Dicerna, Alnylam, Orfan, Cantero, and Chinook; is a scientific advisor for OHF and Dent Disease Foundation; and has received research funding from Dicerna and Alnylam. CL is a consultant for Dicerna, Eli Lilly. PC is on the advisory board of Alnylam and Dicerna. JCL is a consultant for Alnylam, Dicerna, OxThera, BridgeBio/Cantera, Chinook, BioMarin, Synlogic, Novobiome, Oxidien, Federation Bio, Intellia, and Precision BioSciences; has received research funding from OxThera, Allena, Siemens, Alnylam, Dicerna, Synlogic, Novobiome, and Arkray. SHM has received honoraria from Shire, Sanofi, and PeerVoice; and is a scientific advisor for Dicerna and Alnylam. SH has received research funding from Dicerna and honoraria from Olympus, Boston Scientific, and Becton Dickinson. GA is a consultant for and has received honoraria from AstraZeneca Alexion, Recordati, Chiesi, Kyowa Kirin, and Advicenne; is a consultant for Dicerna and Alnylam; and is a scientific advisor for AstraZeneca Alexion. ATR has received honoraria from Alnylan. TAF has received

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DATA STATEMENT

Because of the sensitive nature of the data collected for this study, the dataset will not be made available to other researchers. For additional study details, please visit www.clinicalTrials.gov (https://www.clinicaltrials.gov/ct2/show/NCT03847909).

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

PHYOX2 study investigators and safety review committee.
Supplementary Methods.
Table S1. Definition of study endpoints.
Table S2. Summary of protocol amendments.
Table S3. Sensitivity analysis of the primary and secondary endpoints
Table S4. *Post hoc* sensitivity analysis of the primary endpoint (exclusion of participants with baseline Uox >2.8 mmol/24 h; modified intent-to-treat [mITT] population).
Table S5. Treatment-related adverse events (AEs) in patients with primary hyperoxaluria type 1 or 2 who received subcutaneous nedosiran or placebo (safety population).
Supplementary Results.
Figure S1. Flow of participants with primary hyperoxaluria receiving multiple doses of nedosiran or placebo in PHYOX2.
Figure S2. Average percent change from baseline in 24-hour urinary oxalate excretion between day 90 and day 180 (modified intent-to-treat [mITT] population).
Figure S3. Levels of plasma oxalate among adults treated with nedosiran (stratified by estimated glomerular filtration rate [eGFR]).
Supplementary References.

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