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# PHYOX3: Nedosiran Long-Term Safety and Efficacy in Patients With Primary Hyperoxaluria Type 1

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**Introduction:** Primary hyperoxaluria type 1 (PH1) is a rare genetic disease characterized by oxalate overproduction in the liver, leading to hyperoxaluria, calcium oxalate stones, nephrocalcinosis, progressive chronic kidney damage, kidney failure, and systemic oxalate deposition. Nedosiran, an RNA interference therapy against lactate dehydrogenase subunit A mRNA, has been approved in the USA for treating patients with PH1 who are aged ≥ 9 years and have an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min per 1.73 $m^2$. PHYOX3 (NCT04042402) is an open-label extension trial evaluating the long-term safety and efficacy of once-monthly nedosiran in patients with primary hyperoxaluria (PH).

**Methods:** This PHYOX3 interim analysis includes 40 participants with PH1 from PHYOX1 (NCT03392896; $n = 13$) and PHYOX2 (NCT03847909; $n = 27$) trials. Efficacy was assessed using eGFR, urinary oxalate (Uox) excretion, and clinical outcomes. Safety and efficacy of nedosiran were assessed up to 42 months.

**Results:** At baseline, mean (SD) age was 24.9 (9.7) years (55% females; 42.5% White), mean (SD) eGFR was 80.0 (28.6) ml/min per 1.73 $m^2$, and median number of kidney stone events (KSEs) was 3.0. The mean eGFR range throughout the study was 71.1 to 81.5 ml/min per 1.73 $m^2$, and mean 24-hour Uox excretion declined by > 60%, maintained from month 4 to month 42. Annualized stone event rate decreased from 0.40 at baseline to 0.20 (22 events/108.8 person-years). Eight participants experienced ≥ 1 serious adverse events (AEs), none associated with nedosiran. The most common nonserious treatment-related AEs were injection site reactions (6 participants; 15%). Four participants discontinued treatments (1 pregnancy and 3 withdrawals), and no deaths were reported.

**Conclusion:** Nedosiran was well-tolerated, reduced average Uox levels, reduced kidney stone occurrence, and maintained stable renal function for over 3 years.

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PH is a group of 3 (PH1, PH2, and PH3) rare genetic disorders.[1–3] Each PH type is characterized by an enzymatic defect because of pathogenic variants in 3 specific genes (alanine-glyoxylate aminotransferase [*AGXT*; PH1], glyoxylate and hydroxypyruvate reductase [*GRHPR*; PH2], and 4-hydroxy-2-oxoglutarate aldolase 1 [*HOGA1*; PH3]). These defects lead to the overproduction of oxalate, which primarily originates from glyoxylate in the liver.[1,2,4,5]

In PH1, the excess oxalate, after being filtered by the kidneys into the urine, can bind with calcium to form calcium oxalate kidney stones (urolithiasis or nephrolithiasis), or deposit as calcium oxalate crystals within the kidney parenchyma (nephrocalcinosis) leading to oxalate nephropathy, progressive chronic kidney disease (CKD), and eventual kidney

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failure.[1,2,6-8] After kidney function worsens, persistent excessive oxalate production in the liver can accumulate in the body leading to systemic oxalosis, a life-threatening condition in which oxalate deposits in other tissues, including the skin, eyes, bones, and heart.[1-3,8-16]

The RNA interference therapy nedosiran has recently been approved in the USA to lower Uox excretion in patients living with PH1 and relatively preserved renal function (aged ≥ 9 years; eGFR ≥ 30 ml/min per 1.73 $m^2$); use of nedosiran for PH2 and PH3 is currently under investigation.[17] Nedosiran reduces the production of the hepatic enzyme lactate dehydrogenase, by interfering with the translation of the *LDH subunit A* mRNA, thereby limiting the conversion of glyoxylate into oxalate. Given that hepatic lactate dehydrogenase is an essential enzyme involved in the final step of oxalate production in PH1, nedosiran was developed to reduce hepatic oxalate production and Uox excretion in patients with PH1.

This PHYOX3 (NCT04042402) interim analysis aims to evaluate the long-term safety and efficacy of monthly nedosiran administration in participants with PH1 rolling over from the PHYOX1 (NCT03392896) and PHYOX2 (NCT03847909) trials. In the single-dose open-label PHYOX1 study, participants with PH1 and PH2 received 1 of 3 nedosiran doses (1.5, 3.0, and 6.0 mg/kg). Nedosiran treatment was well-tolerated in both groups, resulting in a mean (SD) maximum Uox reduction from baseline of 55% (19.8).[18] PHYOX2 was a double-blind placebo-controlled study where PH1 and PH2 participants received monthly treatments of either nedosiran or placebo for 6 months (same dosing as PHYOX3). The PHYOX2 study showed that nedosiran had a good safety profile and led to least square mean difference of 59% in the percent change from baseline in 24-hour Uox excretion between the nedosiran group and placebo group, averaged over the period from month 3 to 6.[19] Given the initial favorable outcome of nedosiran treatment in previous clinical trials, PHYOX3 aimed to evaluate the long-term safety and efficacy of monthly nedosiran administration. Although PHYOX3 is an ongoing study encompassing all PH subtypes within the entire PHYOX program, this interim analysis focuses on participants with PH1 who have completed PHYOX1 and PHYOX2. The selective focus on PH1 is due to the medication's approval for this specific indication and the supporting long-term data on PH1 participants.[17,20]

## METHODS

### Study Design and Participants

PHYOX3 (NCT04042402) is a multicenter, uncontrolled, open-label extension phase 3 trial evaluating long-term safety and efficacy of monthly nedosiran, herein for participants living with PH who completed a previous trial of nedosiran (across the entire PHYOX program), and PH-affected pediatric siblings of previous nedosiran clinical trial completers. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable national and local regulatory requirements. The study protocol was approved by the independent ethics committees or institutional review boards at each participating site. All participants provided written informed consent before joining PHYOX3 and were recruited between July 2019 and June 2021. After initiating monthly nedosiran treatment, participants were followed-up with until October 30, 2023 (the cut-off for this publication). The full protocol and results for PHYOX1, PHYOX2, and PHYOX3 (first PH1 interim analysis) have been previously published.[18-20]

This new PHYOX3 interim analysis included 40 participants living with PH1, rolling over from PHYOX1 ($n = 13$) or PHYOX2 ($n = 27$) (Figure 1). Key inclusion criteria were as follows: documented PH1 diagnosis, successful completion of 1 of the 2 above-mentioned parent studies, baseline 24-hour Uox

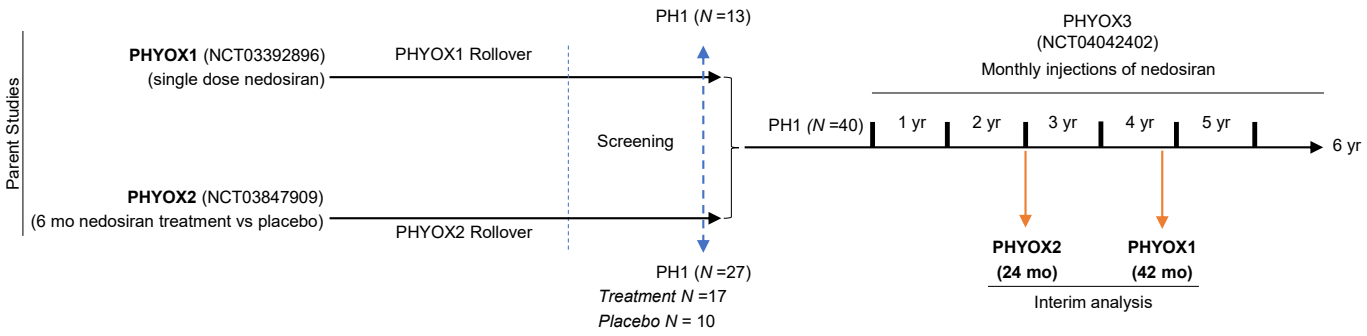


**Figure 1.** PHYOX3 study design and interim analysis group. A total of 40 participants with PH1, rolling over from the PHYOX1 ($n = 13$; NCT03392896) and PHYOX2 ($n = 27$; NCT03847909) trials, initiated a new long-term, once-monthly nedosiran treatment (PHYOX3) lasting up to 6 years. PH1, primary hyperoxaluria type 1.

excretion ≥ 0.7 mmol/d (63 mg/d) for participants aged ≥ 18 years (or ≥ 0.7 mmol/d per 1.73 $m^2$ body surface area [BSA] [63 mg/d per 1.73 $m^2$] for participants aged < 18 years), and eGFR at screening ≥ 30 ml/min per 1.73 $m^2$ BSA at baseline in the PHYOX3 study. For entry into PHYOX3, eGFR at screening was calculated using the CKD-Epidemiology Collaboration equation in adults, or the 2012 formula by Schwartz in participants aged 6 to < 18 years.[21] Key exclusion criteria included plasma oxalate > 30 μmol/l (approximate threshold for increased systemic oxalosis risk), renal or hepatic transplantation (before or planned within the study period), current dialysis, and documented systemic oxalosis manifestation (including preexisting retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations), previous use of other RNA interference drugs (except nedosiran) in the past 6 months, or history of reactions to oligonucleotide-based therapy (i.e., severe thrombocytopenia, hepatotoxicity, severe flu-like symptoms, localized skin reactions, and coagulopathy or clinically significant prolongation of clotting time). Participants receiving oral pyridoxine (vitamin B6) must have been on a stable dose for at least 4 weeks before day 1 and be willing to remain on the same stable dose throughout the study.

## Interventions

In PHYOX3, all 40 participants received a fixed, monthly dose of nedosiran via subcutaneous injection. Nedosiran dosage regimen was based on weight as follows: adults and adolescents (aged 12–17 years) with weight ≥ 50 kg received a fixed dose of 170 mg, whereas they received a fixed dose of 136 mg if weighing < 50 kg. Children (aged 6–11 years) received a weight-based dose of 3.5 mg/kg (not to exceed 170 mg). Nedosiran was administered by study staff at clinic visits up to day 180, when this task could then be performed by the participant (or caregiver) under the supervision of the study staff. An optional at-home administration by participants and/or their caregivers was also allowed after day 180 for months, with no clinic visit required after the participants had been successfully trained and observed doing self-administration. Home visits were available to assist, as necessary.

All participants were asked to continue ongoing standard-of-care measures for PH treatment (e.g., vitamin B6 intake), as well as to avoid vitamin C supplements (including multivitamins) and oxalate-rich foods at all times during the study because of the possible impact on Uox excretion.[22] Nedosiran treatment during PHYOX3 was planned for up to 6 years, or until nedosiran is commercially or otherwise available to a participant.

## Outcomes

The primary objective of PHYOX3 was to evaluate the long-term efficacy and safety of nedosiran. The primary end point was the annual rate of decline in eGFR. Secondary efficacy end points included the following: (i) normalization (< 0.46 mmol/24 h; upper limit of normal [ULN])[23] or near-normalization (≥ 0.46–< 0.60 mmol/24 h; > ULN–< 1.3 × ULN)[18] of Uox excretion (adjusted per 1.73 $m^2$ BSA in all participants) at each time point throughout the study, (ii) absolute and percent maximum reduction in 24-hour Uox excretion from baseline, and (iii) percentage of participants with spot Uox-to-urinary creatinine ratio ≤ ULN or 1.5 × ULN at each time point. Methods to measure Uox and plasma oxalate, and assess ULN for plasma oxalate were as previously published.[20] A key secondary objective was the evaluation of nedosiran safety and tolerability. This was measured by AE monitoring, change from baseline in 12-lead electrocardiogram, physical examination findings, vital signs, and clinical laboratory tests (hematology, serum chemistry, coagulation parameters, and urinalysis). Participants were further monitored for potential risks related to RNA interference molecules, including the following: (i) injection site reactions, (ii) liver abnormalities, (iii) markers of inflammation (cytokine release), and (iv) direct (anti-drug antibodies [ADAs]). AEs of special interest, defined as noteworthy events for the product or product class, included injection site reactions, muscle pain or weakness, and KSEs. AEs were coded using the Medical Dictionary for Regulatory Activities (version 26.0) and graded according to intensity categories. Further secondary objectives were as follows: (i) change from baseline in the number of stone events and stone burden and (ii) advanced CKD and end-stage kidney disease incidence. Advanced CKD was defined as "severe CKD" also known as CKD stage 4 (eGFR = 15–29 ml/min) or end-stage kidney disease also known as CKD stage 5 (eGFR < 15 ml/min per 1.73 $m^2$ BSA in participants aged < 18 years).

As in the previously published PHYOX3 interim analysis, baseline KSE rate was based on participant-provided medical history.[20] For KSE during the study, kidney ultrasound was performed. The kidneys were examined in the longitudinal (sagittal) and transverse scan planes. Participants had a full bladder during image acquisition. Standardized nephrocalcinosis grading (0–3) was performed.[24]

For this study, stone events were defined as all events that meet ≥1 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, and renal colic requiring medication. Finally, quality of life (QOL), pediatric QOL inventory (pedsQL) scores, and 36-item short form health survey (SF-36) parameters were included as exploratory efficacy end points.

### Analysis Populations

The safety population included all participants who received at least 1 dose of nedosiran. All safety and efficacy analyses were performed on this group.

### Statistics

This interim analysis included data through October 2023, which covers nearly 4 years of the PHYOX3 study, with participants rolled over from PHYOX1 and PHYOX2 receiving nedosiran treatment for a total of 42 months and 24 months in PHYOX3 study. Summary statistics for continuous variables included mean, SD, SEM, and median (minimum, maximum). Categorical variables are presented as number and percentage of participants ($n$ [%]). All analyses were performed using Statistical Analysis System (SAS; version 9.4; SAS Institute Inc., Cary, NC). Participants with missing data were excluded from the summary of the variable.

## RESULTS

### Participants

A total of 13 out of 15 participants with PH1 rolled over from PHYOX1; the remaining 2 PHYOX1 participants did not enroll in PHYOX3 and instead elected to initiate treatment with lumasiran (OXLUMO; Alnylam Pharmaceuticals, Cambridge, MA), which was commercially available by the start of PHYOX3. A total of 27 out of 29 participants with PH1 rolling over from PHYOX2 trial were enrolled in PHYOX3 trial. Two PHYOX2 participants (1 from each treatment group) were not included due to early withdrawal (1 due to worsening kidney function requiring dialysis initiation, and the other one due to a cardiac-related serious AEs).

As of this cut-off date, 36 out of 40 participants initially enrolled in PHYOX3 were still on treatment, and none have withdrawn due to AEs. A total of 4 participants withdrew, 1 because of pregnancy, 1 because of participant choice, and 2 were withdrawn by their local principal investogator (1 because of worsening renal failure and subsequent switch to lumasiran, and the other for unknown reasons) (Table S1).

At the PHYOX3 baseline, the mean (SD) and median (range) age of the overall population was 24.9 (9.7) years and 23.0 (10–46) years, respectively. Three participants (7.5%) were children (aged 6–11 years), 8 participants (20%) were aged 12 to 17 years, and 29 (72.5%) were aged ≥ 18 years. Twenty-two participants (55%) were female, and 17 (42.5%) were White. At baseline, mean (SD) eGFR was 80.0 (28.6) ml/min per 1.73 $m^2$. Most participants (33 [82.5%]) had an eGFR ≥ 45 ml/min per 1.73 $m^2$, and 7 (17.5%) had an eGFR between 30 and 45 ml/min per 1.73 $m^2$. Mean (SD) 24-hour Uox excretion was 1.5 (0.64) mmol/d per 1.73 $m^2$. Most of the participants with available CKD data were in stage 1 (18 [45%]), whereas 11 (27.5%) and 8 (20%) were in stages 2 and 3B, respectively. Thirteen participants (32.5%) reported KSE in the last 12 months before baseline. The median number of kidney stones at baseline was 3.0. Stable Vitamin B6 use at baseline was reported by 26 participants (65%) (Table 1).

### Efficacy

#### *eGFR*

Mean eGFR remained stable (range: 71.1–81.5 ml/min per 1.73 $m^2$) in the PH1 rollover cohort (Figure 2) through the longest follow-up of 42 months (from PHYOX1; Figure S1A) and 24 months (from PHYOX2; Figure S1B). Although most participants remained stable throughout the study, 3 of them (7.5%), out of the 7 (17.5%) who had an eGFR between 30 and 45 ml/min per 1.73 $m^2$ at baseline (Table 1), experienced a decline in renal function. Conversely, the other 4 (10%) improved or remained stable.

#### *Uox*

Nedosiran treatment during PHYOX3 led to rapid (≤ 3 months) reduction of 24-hour Uox excretion to normal (< 0.46 mmol/24 h [< 40.57 mg]; ULN) or near-normal (≥ 0.46–< 0.60 mmol/24 h [≥ 40.57–< 52.81 mg]; > ULN–< 1.3 × ULN) levels throughout the study period (Figure 3a). In the PH1 rollover group, the mean percent reduction in 24-hour Uox excretion was maintained at least 60% starting from month 2 (Figure 3b). Similarly, when participants from PHYOX1 and PHYOX2 study rollovers were considered separately, nedosiran treatment resulted in decreased absolute and percent 24-hour Uox excretion for both groups (Figure S2A–D). Patients who had already received nedosiran treatment in PHYOX2 (treatment parent study) experienced an initial reduction in Uox levels before entering PHYOX3. As a result, this subgroup had lower Uox baseline levels and a smaller percentage reduction during the PHYOX3 study than the treatment-naive subgroup (placebo in PHYOX2 parent study) (Figure S2C and D). However, although the 2 groups eventually reached similar Uox levels, the higher reduction rate in the treatment-naive subgroup

**Table 1.** Demographics and baseline characteristics

| Category | PHYOX1 rollover | PHYOX2 rollover: Treated in p.s. | PHYOX2 rollover: Placebo in p.s. | Total |
|---|---|---|---|---|
| Age (yrs) | | | | |
| *n* | 13 | 17 | 10 | 40 |
| Mean (SD) | 24.2 (6.64) | 26.4 (11.25) | 23.3 (10.86) | 24.9 (9.72) |
| Median | 23.0 | 23.0 | 21.5 | 23.0 |
| Min, Max | 14, 39 | 10, 46 | 11, 37 | 10, 46 |
| Age group, *n* (%) | | | | |
| 6–11 yrs | 0 | 1 (5.9) | 2 (20.0) | 3 (7.5) |
| 12–17 yrs | 2 (15.4) | 3 (17.6) | 3 (30.0) | 8 (20.0) |
| ≥ 18 yrs | 11 (84.6) | 13 (76.5) | 5 (50.0) | 29 (72.5) |
| Gender, *n* (%) | | | | |
| Male | 6 (46.2) | 7 (41.2) | 5 (50.0) | 18 (45.0) |
| Female | 7 (53.8) | 10 (58.8) | 5 (50.0) | 22 (55.0) |
| Race, *n* (%)[a] | | | | |
| Asian | 1 (7.7) | 4 (23.5) | 0 | 5 (21.7) |
| Black or African American | 0 | 0 | 1 (10.0) | 1 (4.3) |
| White | 6 (46.2) | 6 (35.3) | 5 (50.0) | 17 (73.9) |
| Not available | 6 (46.2) | 7 (41.2) | 4 (40.0) | 17 (42.5) |
| Ethnicity, *n* (%) | | | | |
| Hispanic or Latino | 0 | 2 (11.8) | 0 | 2 (5.0) |
| Not Hispanic or Latino | 9 (69.2) | 14 (82.4) | 8 (80.0) | 31 (77.5) |
| Not available | 4 (30.8) | 1 (5.9) | 2 (20.0) | 7 (17.5) |
| Baseline eGFR (ml/min/SSA)[b] | | | | |
| *n* | 13 | 17 | 10 | 40 |
| Mean (SD) | 75.54 (22.14) | 84.35 (35.16) | 78.50 (25.22) | 80.03 (28.65) |
| Median | 78.00 | 86.00 | 80.50 | 83.00 |
| Min, max | 36.0, 114.0 | 36.0, 151.0 | 49.0, 115.0 | 36.0, 151.0 |
| eGFR category | | | | |
| ≥ 30 and < 45 ml/min/SSA, *n* (%) | 2 (15.4) | 4 (23.5) | 0 | 7 (17.5) |
| ≥ 45 ml/min/SSA, *n* (%) | 11 (84.6) | 13 (76.5) | 10 (100) | 33 (82.5) |
| Baseline adjusted 24-h urinary oxalate (mmol/d) in parent study[c] | | | | |
| *n* | 13 | 17 | 10 | 40 |
| Mean (SD) | 1.3 (0.54) | 1.3 (0.45) | 2.0 (0.83) | 1.4 (0.64) |
| Median | 1.1 | 1.3 | 1.7 | 1.3 |
| Min, max | 0.8, 2.2 | 0.8, 2.3 | 0.9, 3.7 | 0.8, 3.7 |
| Time since PH diagnosis (yrs)[d] | | | | |
| *n* | 13 | 17 | 10 | 40 |
| Mean (SD) | 15.74 (5.40) | 8.25 (7.57) | 7.83 (8.85) | 10.57 (7.99) |
| Median | 15.55 | 5.36 | 3.85 | 8.09 |
| Min, max | 4.12, 25.07 | 0.53, 22.25 | 0.94, 27.21 | 0.53, 27.21 |
| Chronic kidney disease stage, *n* (%)[e] | | | | |
| Stage 1 | 3 (23.1) | 10 (58.8) | 5 (50.0) | 18 (45.0) |
| Stage 2 | 5 (38.5) | 4 (23.5) | 2 (20.0) | 11 (27.5) |
| Stage 3A | 0 | 0 | 1 (10.0) | 1 (2.5) |
| Stage 3B | 3 (23.1) | 3 (17.6) | 2 (20.0) | 8 (20.0) |
| Missing | 2 (15.4) | 0 | 0 | 2 (5) |
| Any kidney stone event in last 12 mos, *n* (%)[f] | | | | |
| Yes | 1 (7.7) | 7 (41.2) | 5 (50.0) | 13 (32.5) |
| No | 12 (92.3) | 10 (58.8) | 5 (50.0) | 27 (67.5) |
| Number of kidney stone events in last 12 mos[f] | | | | |
| *n* | 1 | 7 | 5 | 13 |
| Mean (SD) | 1.0 (-) | 1.4 (0.79) | 1.0 (0.00) | 1.2 (0.60) |
| Median | 1.0 | 1.0 | 1.0 | 1.0 |
| Min, max | 1, 1 | 1, 3 | 1, 1 | 1, 3 |
| Number of kidney stones at baseline[a] | | | | |
| *n* | 0 | 12 | 9 | 21 |
| Mean (SD) | - | 3.0 (2.56) | 6.6 (10.38) | 4.5 (7.07) |
| Median | - | 2.0 | 3.0 | 3.0 |
| Min, max | - | 1, 9 | 1, 34 | 1, 34 |
| Surface area of kidney stones at baseline ($mm^2$)[b] | | | | |
| *n* | 0 | 12 | 9 | 21 |
| Mean (SD) | - | 107.8 (134.39) | 114.0 (105.02) | 110.5 (119.81) |
| Median | - | 56.0 | 71.0 | 71.0 |
| Min, max | - | 21, 494 | 2, 296 | 2, 494 |
| Vitamin B6 intake, *n* (%) | | | | |
| Yes | 7 (53.8) | 11 (64.7) | 8 (80.0) | 26 (65.0) |
| No | 6 (46.2) | 6 (35.3) | 2 (20.0) | 14 (35.0) |

BSA, body surface area; eGFR, estimated glomerular filtration rate; PH, primary hyperoxaluria; p.s., parent study; SSA, surface area; Uox, urinary oxalate.
[a]Percentages in the total column relate to the percentage of participants for whom race data was available.
[b]Baseline is defined as the last nonmissing value before the first dose of PHYOX3 study intervention for participants rolling over from PHYOX1/PHYOX2 studies and siblings not previously enrolled in a PHYOX study.
[c]Baseline 24-h Uox was calculated as the average of the 2 screening results for participants rolling over from PHYOX1/PHYOX2 studies and siblings not previously enrolled in a PHYOX study. BSA-adjusted 24-h Uox values were used for all participants. BSA-adjusted 24-hour Uox = 24-h Uox value × (1.73/BSA of participant).
[d]Time since PH diagnosis (yrs) was defined as (date of informed-consent signature–date of PH diagnosis + 1)/365.25. PH diagnosis dates with partial dates were imputed as follows: missing day values were imputed as 15, and missing month values were imputed as June.
[e]Data derived from PHYOX3 baseline for participants rolling over from PHYOX1 study, and PHYOX2 baseline for participants rolling over from PHYOX2 study.
[f]For participants rolling over from PHYOX1/PHYOX2 studies and siblings not previously enrolled in a PHYOX study, noncurrent KSEs in the last 12 mo were those events that had a start date within 12 mo before the date of informed-consent signature for PHYOX3 study. For participants rolling over from PHYOX2 study, the kidney stone event history data of PHYOX2 was used. Kidney stone event start dates with partial dates were as follows: missing day values were imputed as 15, and missing month values were imputed as June.

is to be expected due to their higher baseline levels at the beginning of PHYOX3.

Starting at month 2, 11 participants (91.7%) with PH1 from PHYOX1 rollover group reached a normal or near-normal 24-hour Uox excretion, and at least 10 participants (76.9%) maintained a reduced Uox until month 42 (Figure S3A). In contrast, 12 of PH1 participants (75%) (treatment in PHYOX2 parent study) subgroup reached normal or near-normal 24-hour Uox excretion at month 3, and at least 9 participants (60%) remained stable throughout the study (Figure S3B). Finally, 2 participants (22.2%) from the treatment-naive (placebo in PHYOX2 parent study) subgroup reached near-normal 24-hour Uox excretion at month 6, with the highest proportion of participants (6 [75%])

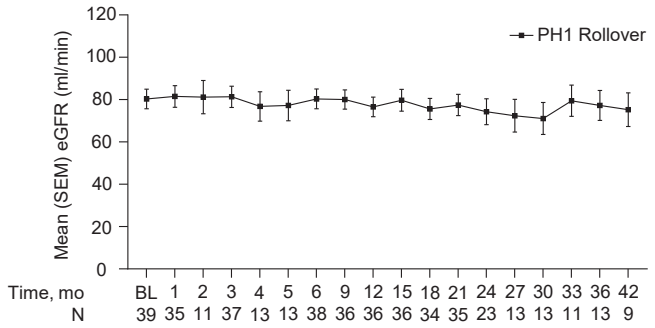


**Figure 2.** Mean eGFR throughout PHYOX3 study. Mean (± SEM) eGFR at PHYOX3 baseline and throughout the study. PH1 rollover includes data from PHYOX1 and PHYOX2. Note: Number of participants assessed at each time point is shown below the graph. eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1.

reaching normal or near-normal excretion levels at month 24 (Figure S3B).

Of the 3 participants who experienced decreased renal function during the study, 24-hour Uox majorly decreased for 2 of them.

Owing to normalization of Uox excretion on 3 consecutive visits, a total of 22 participants (56.4%) were eligible for reduction of hyperhydration and discontinuation of other comedications during the study at any visit (Table S2).

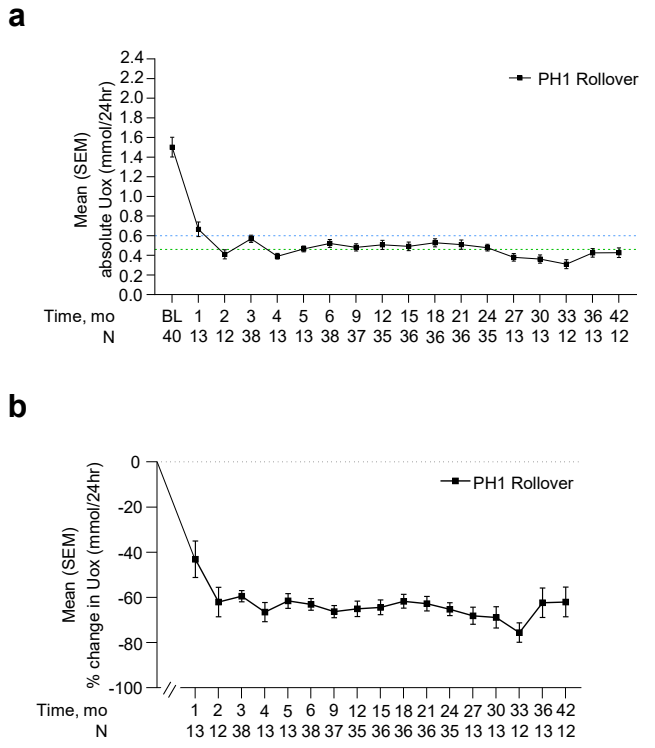


**Figure 3.** Mean absolute change, percent change, and maximum percent reduction in 24-hour Uox from baseline in PHYOX3 study. (a) Mean (± SEM) absolute Uox at PHYOX3 baseline and throughout the study. Dotted lines indicate normal (green) and near-normal (blue) limits.(b) Mean (± SEM) percentage Uox at PHYOX3 baseline and throughout the study. PH1 rollover includes data from PHYOX1 and PHYOX2. Note: Double line on the x-axis represents the end of the previous study period. The number of participants assessed at each time point is shown below the graph. PH1, primary hyperoxaluria type 1; Uox, urinary oxalate.

## Stone Burden

The baseline annualized stone event rate was 0.40 (13 participants [32.5%], 16 events, 40 years exposed) based on recall data provided by participants. The annualized stone event rate based on posttreatment clinical data collected during the study period was 0.20 (11 participants [27.5%], 22 events, 108.8 years exposed) (Table 2). Only 1 out of 26 KSEs was not resolved by the data cutoff date. At baseline, 32 out of 39 participants (82.1%) showed no evident nephrocalcinosis, whereas 7 participants (17.9%) presented with grade 1 nephrocalcinosis. By month 18, 7 out of 33 participants (21.2%) exhibited grade 1 nephrocalcinosis. The data from the 6 participants with no evident nephrocalcinosis at baseline were missing at month 18 (Table S3).

## Kidney Functions

Throughout the study, 3 adult participants (7.5%) rolling over from PHYOX1 experienced a decline in renal function (2 of which were $< 45$ ml/min per 1.73 $m^2$), with 2 developing severe CKD (eGFR = 15–29 ml/min) and 1 developing end-stage kidney disease (eGFR $< 15$ ml/min per 1.73 $m^2$ BSA in participants aged $< 18$ years) (Table S4).

**Table 2.** Annual rate of kidney stone events

| Category | PHYOX1 rollover | PHYOX2 rollover | | Total |
|---|---|---|---|---|
| | | Treated in p.s. | Placebo in p.s. | |
| Kidney stone events in last 12 months at baseline[a] | | | | |
| Number of participants with events, *n* (%) | 1 (7.7) | 7 (41.2) | 5 (50.0) | 13 (32.5) |
| Total number of events | 1 | 10 | 5 | 16 |
| Total number of years exposed | 13 | 17 | 10 | 40 |
| Annualized stone event rate | 0.0769 | 0.5882 | 0.5000 | 0.4000 |
| Kidney Stone Events during study period[b] | | | | |
| Number of participants with events, *n* (%) | 6 (46.2) | 2 (11.8) | 3 (30.0) | 11 (27.5) |
| Total number of events | 14 | 4 | 4 | 22 |
| Total number of years exposed | 47.79 | 39.29 | 21.69 | 108.8 |
| Annualized stone event rate | 0.2929 | 0.1018 | 0.1844 | 0.2023 |

p.s., parent study.
[a]For participants rolling over from PHYOX1 study and siblings not previously enrolled in a PHYOX study, noncurrent KSEs in the last 12 mo are those events that have a start date within 12 mo before the date of informed consent signature for the PHYOX3 study. For participants rolling over from PHYOX2 study, the KSE history data of PHYOX2 is used. Kidney stone event start dates with partial dates will be imputed as follows: missing day values were imputed as 15, and missing month values were be imputed as June.
[b]Number of years exposed during study period is the total elapsed time between the first dose date and last day of visit in the study, divided by 365.25. Annualized stone event rate (number of noncurrent stone events/yr/person) is derived as number of stone events in the exposure period/total number of years exposed.

## Safety

A total of 39 participants (97.5%) experienced ≥1 AEs, most of which were mild (17 [42.5%]) or moderate (19 [47.5%]) in severity. A total of 3 participants (7.5%) reported severe AEs, including kidney stones, pain in left arm, pyelonephritis associated with a preexisting kidney stone, acute kidney injury, and kidney failure. A total of 24 (60%) had treatment-related AEs, none of which were serious (Table 3). Eight out of 40 participants (20%) experienced ≥ 1 serious AEs, none of which were associated with nedosiran treatment and many of which were due to a hospital stay because of other complications. Seventeen participants (42.5%) reported AEs of special interest, including injection site reactions (6 [15%]), muscle pain or weakness (1 [2.5%]), and KSEs (11 [27.5%]) (Table 3). Except for one KSE, all other AEs of special interest were resolved during the study. There were no deaths or AEs leading to discontinuation of the study drug to date (October 2023 cut-off). No other significant laboratory value trends were noted. Only 2 out of 31 participants (5%) (rolling over from PHYOX2 nedosiran-treatment subgroup) had detectable ADAs at baseline in the parent study, but no treatment-emergent ADA were detected. During PHYOX3 trial, both participants were negative for ADAs at day 45, whereas 1 had detectable antibodies throughout the study (Table S5). Despite this transient presence of ADAs, none of the positive participants experienced an impact in nedosiran-mediated efficacy or safety (data not shown).

**Table 3.** Overall summary of adverse events

| Variable | PHYOX1 rollover *n* (%) | PHYOX2 rollover | | Total *n* (%) |
|---|---|---|---|---|
| | | Treated in p.s. *n* (%) | Placebo in p.s. *n* (%) | |
| Number of subjects reporting at least 1[a] | | | | |
| Any AE | 13 (100) | 16 (94.1) | 10 (100) | 39 (97.5) |
| Treatment-related AE | 10 (76.9) | 7 (41.2) | 7 (70.0) | 24 (60.0) |
| Severity | 13 (100) | 16 (94.1) | 10 (100) | 39 (97.5) |
| Mild | 3 (23.1) | 7 (41.2) | 7 (70.0) | 17 (42.5) |
| Moderate | 8 (61.5) | 9 (52.9) | 2 (20.0) | 19 (47.5) |
| Severe | 2 (15.4) | 0 | 1 (10.0) | 3 (7.5) |
| Deaths | 0 | 0 | 0 | 0 |
| SAE | 4 (30.8) | 3 (17.6) | 1 (10.0) | 8 (20.0) |
| Treatment-related SAE | 0 | 0 | 0 | 0 |
| AE of special interest[b] | 9 (69.2) | 5 (29.4) | 3 (30.0) | 17 (42.5) |
| Injection site reaction | 3 (23.1) | 3 (17.6) | 0 | 6 (15.0) |
| Grade 1 | 2 (15.4) | 3 (17.6) | 0 | 5 (12.5) |
| Grade 2 | 1 (7.7) | 0 | 0 | 1 (2.5) |
| Muscle pain or weakness | 1 (7.7) | 0 | 0 | 1 (2.5) |
| Mild | 1 (7.7) | 0 | 0 | 1 (2.5) |
| Kidney stone events | 6 (46.2) | 2 (11.8) | 3 (30.0) | 11 (27.5) |
| Mild | 3 (23.1) | 0 | 2 (20.0) | 5 (12.5) |
| Moderate | 2 (15.4) | 2 (11.8) | 0 | 4 (10.0) |
| Severe | 1 (7.7) | 0 | 1 (10.0) | 2 (5.0) |

AEs, adverse events; SAEs, serious adverse events; p.s., parental study.
Note: A treatment-related AE is defined as any adverse event that begins on or after the first dose of study intervention for PHYOX3 and through the PHYOX3 study completion date from the end of study case report form. Treatment-related AEs are considered to be related to study intervention if they are marked as possibly, probably, or definitely related to the study intervention on the case report form. Treatment-related AEs are considered as leading to discontinuation if the action taken is marked as "drug withdrawn" on the case report form. Treatment-related AEs are considered to be treated if the action taken is marked as either a new over the counter or prescription drug added, or nondrug therapy on the case report form. Treatment-related AEs are considered to be resolved if the outcome marked is either recovered/resolved or recovered/resolved with sequelae on the case report form. The denominator used for the percentages is the total number of subjects with events.
[a]The denominator used for the percentages is the number of subjects in the Safety Population.
[b]AEs of special interest include injection site reactions, muscle pain and weakness, and kidney stones.

## QOL

The analysis of the PedsQL scores indicates that participants experienced various changes in their emotional, physical, psychosocial, educational, and social functioning over the 24-month period. These changes suggest that nedosiran treatment had a certain level of positive impact on the overall QOL of the PH1 participants (Table S6). Overall, the PedsQL scores for the PHYOX2 nedosiran-treatment subgroup showed a tendency toward improvement over the 2-year period. For example, there were increases in emotional and physical functioning scores, mean (SD) from 76.250 (17.500) at baseline to 91.667 (14.434) at month 24 and from 86.719 (16.997) to 96.875 (5.413), respectively. Conversely, the PHYOX2 treatment-naive subgroup exhibited a slight tendency toward decreased scores in some areas, such as emotional functioning, mean (SD) from 78.000 (16.432) at baseline to 73.333 (29.297) at month 24 (Table S6). For the PHYOX1 rollover group, the sample size was too small ($n = 1$) to evaluate these changes.

The SF-36 parameters for participants aged ≥ 18 years showed a general trend of stability, with no significant declines in any of the measured domains. The mental component summary score showed a slight decrease, mean (SD) from 47.627 (10.774) at baseline to 42.337 (15.123) at month 24. However, the physical component summary score remained stable (Table S6). For the pain domain scale, mean (SD) at baseline was 0.251 (0.817), and month 24 mean (SD) was 0.093 (0.913), indicating a slight decrease. The vitality domain scale had a baseline mean (SD) of −0.021 (0.976) and a month 24 mean (SD) of −0.277 (1.067), indicating a slight decrease.

# DISCUSSION

This interim analysis of the PHYOX3 (NCT04042402) trial provides valuable insights into the long-term safety and efficacy of nedosiran in 40 participants with PH1, regardless of their previous treatment status with nedosiran. The results demonstrate that nedosiran treatment was well-tolerated, reduced average Uox

excretion to normal or near-normal levels, reduced kidney stone occurrence, and helped participants maintain stable renal function for over 3 years.

However, a group of 3 participants (7.5%) showed a continued decline in renal function. These participants, all rolling over directly from PHYOX1, already presented low eGFR levels ($\geq$ 30 and $<$ 45 ml/min per 1.73 $m^2$) at the PHYOX3 baseline, despite having received a single treatment with nedosiran in the parental study. This suggests that while nedosiran is effective for many, those with significantly compromised renal function at baseline may still experience a decline. This highlights the importance of early diagnosis and treatment to help preserve renal function. An ongoing study includes participants with an eGFR $<$ 30 ml/min to evaluate the efficacy of nedosiran for preserving kidney function in this group with baseline stage 4 CKD (NCT04580420).

Normalization or near-normalization of 24-hour Uox excretion was achieved for most participants from month 2 onward. The efficacy of PHYOX3 for decreasing Uox excretion is in line with the previous PHYOX1 and PHYOX2 studies.[18,19] Despite the 3 participants with declining renal function throughout the study, both 24-hour Uox excretion and Uox-to-urinary creatinine ratio reduced significantly in the 2 participants who developed CKD, while no major changes were observed for the participant with end-stage kidney disease. Urinary citrate-to-creatinine levels remained stable for all 3 participants.

Notably, the PHYOX2 treatment-naive subgroup that previously received placebo in the PHYOX2 trial exhibited less favorable results than the group that received nedosiran treatment. This discrepancy can be attributed to the duration of nedosiran exposure, with the latter group having an additional 6 months of treatment before the commencement of the PHYOX3 trial. Furthermore, the relative lag effect in achieving normal or near-normal Uox levels in the PHYOX2 treatment-naive subgroup may be related to the higher Uox levels at PHYOX3 baseline. In addition, despite having received only 1 dose of nedosiran during the parent study, participants from PHYOX1 rollover showed the most robust outcomes in PHYOX3, being exposed to nedosiran earlier on and for an extended period (42 months). These findings underscore the significance of long-term treatment duration with nedosiran in achieving optimal therapeutic outcomes in participants with PH1. This could suggest that earlier initiation and sustained treatment with nedosiran could be crucial in managing PH1 effectively.

Kidney stones, a major complication of PH1 leading to chronic kidney damage,[1,2] pose a considerable health burden. This interim analysis offers encouraging data, showing no increase in the stone event rate compared with baseline. Participants with a decline in renal function experienced a general increase in kidney stones. However, it is possible that the stone events during the study period are to be attributed to the release of preexisting stones rather than the formation of new stones.

During the PHYOX3 study period (up to month 18), there was a notable decrease in nephrocalcinosis for participants rolling over from PHYOX1. Conversely, for participants rolling over from PHYOX2, nephrocalcinosis either remained stable (treatment-naive subgroup) or increased (nedosiran-treatment subgroup). However, it is important to highlight that nephrocalcinosis assessment based on ultrasound imaging, presents challenges. Variability and low reliability in ultrasound-based evaluations, coupled with the arbitrary nature of nephrocalcinosis grading, cannot ensure that a trend over time occurred.

In this interim analysis, 22 PHYOX3 participants (56.4%) were eligible for reduction of hyperhydration regimens, one of the most burdensome aspects of PH1 treatment.[25] Furthermore, analysis of the QOL data suggested a positive trend for PedsQL scores from baseline to month 24, whereas the SF-36 parameters for subjects aged $\geq$ 18 years remained generally stable. Overall, these results indicate that nedosiran has a potential impact in reducing the burden of PH1 and improving the QOL for participants.[26]

The safety profile of nedosiran was favorable, with no serious treatment-related AEs reported. The most common treatment-related AEs were injection site reactions, which occurred in 15% of participants. No new safety concerns were identified. These findings suggest that nedosiran is a well-tolerated and effective long-term treatment option for participants with PH1.

In conclusion, this interim analysis of the PHYOX3 trial provides strong evidence for the long-term safety and efficacy of nedosiran in patients with PH1 for reducing Uox excretion. Further research is needed to evaluate the longer-term effects of nedosiran on renal function and other associated clinical outcomes such as KSEs in patients with PH1.

## DISCLOSURE

JCL is a consultant for Alnylam, Arbor, Dicerna, OxThera, Allena, Siemens, American Board of Internal Medicine, Lumen, Orfan, Synlogic, Novobiome, Oxidien, Federation Bio, Chinook, BioMarin, Intellia, Novo Nordisk, and Mirium; has received research funding from OxThera, Retrophin, Allena, Siemens, Alnylam, Dicerna, Siemens, Synlogic, Novobiome; Novo Nordisk; received speaking honorarium fees from the American Board of Internal

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## AUTHOR CONTRIBUTIONS

ALSL, BH, GS, JWG, JZ, and VR were involved in data interpretation. BH and JWG were involved in conceptualization. ALSL and GS were involved in data curation. JZ was involved in formal statistical analysis. ALSL, GA, GL, GS, JCL, JWG, SET, and SHM recruited participants to the study. All the authors were involved in writing (reviewing and editing) the manuscript.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** Mean eGFR throughout PHYOX3 study.

**Figure S2.** Mean absolute change, percent change, and maximum percent reduction in 24-hour Uox from baseline in PHYOX3 study.

**Figure S3.** Percentage of participants with normalization or near-normalization of Uox excretion throughout PHYOX3 study.

**Table S1.** Subject disposition.

**Table S2.** Proportion of participants with hyperhydration eligibility during study.

**Table S3.** Proportion of participants with nephrocalcinosis during study.

**Table S4.** Proportion of participants with severe CKD or ESKD.

**Table S5.** Summary of antidrug antibody test results.

**Table S6.** Summary of QOL scores.

CONSORT Checklist.

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