The PHYOX Clinical Program for Primary Hyperoxaluria

Alexandra Haagensen, Jason Russak, Michael Pace, Richard Tenpenny

Dicerna Pharmaceuticals, Inc., Lexington, MA, United States

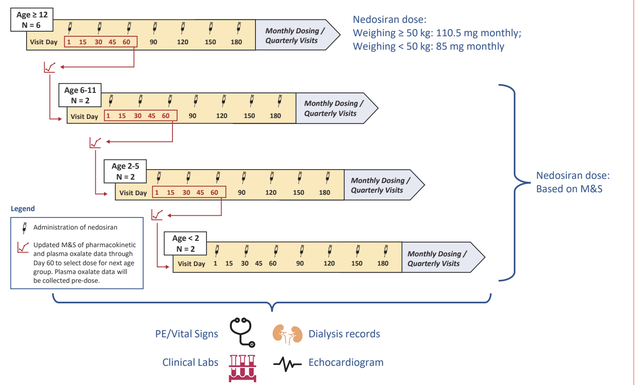
BACKGROUND

Primary hyperoxaluria (PH) is a family of three (PH1, PH2, PH3) ultra-rare, autosomal recessive genetic disorders of hepatic glyoxylate metabolism characterized by overproduction of oxalate and deposition of calcium oxalate stones and/or nephrocalcinosis, leading to progressive kidney damage and, quite often, kidney failure. An increase in plasma oxalate (Pox) leads to oxalate deposition in extrahepatic tissues in a process called systemic oxalosis. Oxalosis is primarily observed in the bones, retina, blood vessels, myocardium, and skin and is associated with high morbidity and mortality. Nedosiran is an investigational ribonucleic acid interference (RNAi) therapy in development for PH under the PHYOX program. Administered once monthly by subcutaneous injection, nedosiran reduces the overproduction of oxalate by reducing levels of hepatic lactate dehydrogenase enzyme (encoded by the *LDHA* gene).

OBJECTIVE

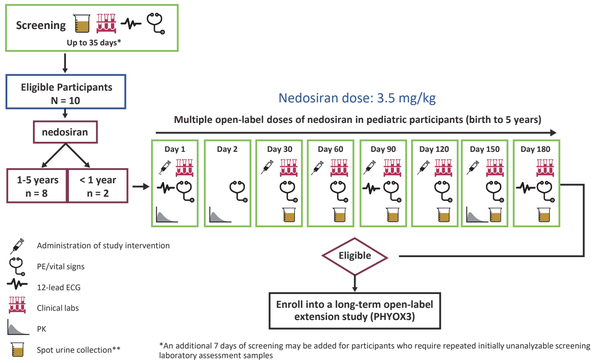
This poster provides an overview of three ongoing clinical trials in the PHYOX program: PHYOX7 (NCT04580420), PHYOX8 (NCT05001269), PHYOX-OBX (NCT04542590)

Figure 1: PHYOX7 Study Design



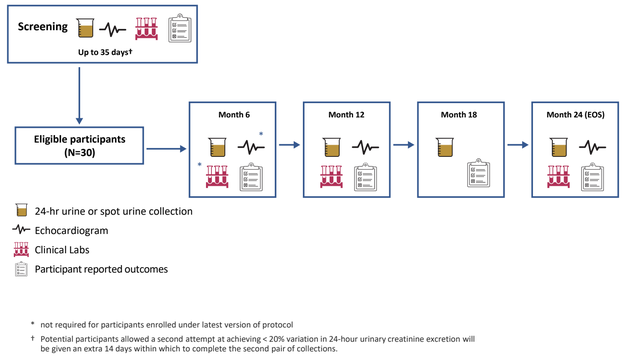
Abbreviations: M&S: modeling and simulation; PE: Physical examination

Figure 2: PHYOX8 Study Design



Abbreviations: PE: Physical examination; ECG: Electrocardiogram; PK: Pharmacokinetics

Figure 3: PHYOX-OBX Study Design



Abbreviations: EOS: end of study

Table 1: PHYOX7 Study Description

Study Design	Open-label, multi-dose, Phase 2	
Number of Participants	12	
Objective	To evaluate safety and efficacy of nedosiran in patients with PH1 or PH2 and severe renal impairment, with or without dialysis	
Duration of Participation	6-month treatment period with up to 3 years of extended follow-up (Figure 1)	
Key Enrollment Criteria	*Inclusion* • Male or female (all ages) with genetically confirmed PH1 or PH2 • eGFR < 30 mL/min/ 1.73 m^2 • Median of 3 Pox values > 30 µmol/L at screening • Stable dialysis regimen for ≥ 3 months prior to screening	*Exclusion* • Prior or planned (within 6 months) hepatic transplantation • Planned renal transplantation (within 6 months); prior renal transplantation allowed • History of severe systemic oxalosis • On dialysis for > 1.5 years
Key Endpoints	*Primary* • Absolute and percent change in Pox from Baseline to Day 180	*Secondary* • Incidence and severity of TEAEs and SAEs • Change in duration and number of dialysis sessions from Baseline to Month 12 • Change in nephrocalcinosis scores over time

Why is this study important?
A significant proportion of patients with PH1 or PH2 progress to end-stage renal disease requiring intensive dialysis procedures and, eventually, renal and/or hepatic transplantation. Nedosiran treatment in the renally impaired population has the potential benefit to reduce or eliminate the excess oxalate production in the liver and thus avoid the need for organ transplantation.

Abbreviations: eGFR: estimated glomerular filtration rate; Pox: plasma oxalate; TEAE: treatment-emergent adverse event; SAE: serious adverse event

Table 2: PHYOX8 Study Description

Study Design	Open-label, multi-dose, Phase 2	
Number of Participants	10	
Objective	To evaluate the safety, efficacy, and pharmacokinetics of nedosiran in pediatric patients (birth to 5 years of age) with PH (PH1, PH2, or PH3*) and relatively intact renal function	
Duration of Participation	6-month treatment period with eligibility to enroll in long-term extension trial (PHYOX3)	
Key Enrollment Criteria	*Inclusion* • Male or female (birth to 5 years of age) with genetically confirmed PH1, PH2, or PH3 • Body weight ≥ 10 kg • Screening average Uox-to-creatinine ratio above 2 times the 95th percentile for age** • eGFR ≥ 30 mL/min/1.73 m^2	*Exclusion* • Hepatic or renal transplantation (prior or planned within study period) • Current or planned dialysis during study period • Screening Pox > 30 µmol/L • Evidence of severe systemic oxalosis
Key Endpoints	*Primary* • The incidence and nature of TEAEs and SAEs	*Secondary* • Percent and absolute change from Baseline to Month 6 in Uox-to-creatinine ratio • Percentage of participants with spot Uox-to-creatinine ratio ≤ ULN and ≤ 1.5 x ULN at any time point through Month 6 • Change from Baseline in eGFR at Month 6

Why is this study important?
PH is a genetic disorder, which means that the overproduction of oxalate begins early in life. To avoid deterioration of renal function and the systemic manifestations of oxalate build-up, treatment for PH should commence as early as possible. It is therefore important to study the safety and efficacy of nedosiran in young children.

*Patients with PH3 only eligible to enroll outside US; **as defined by Matos et al. *Am J Kidney Dis.* 1999;34(2):e1.
Abbreviations: eGFR: estimated glomerular filtration rate; Pox: plasma oxalate; TEAE: treatment-emergent adverse event; SAE: serious adverse event; Uox: urinary oxalate; ULN: upper limit of assay normal

Table 3: PHYOX-OBX Study Description

Study Design	Observational, natural history study	
Number of Participants	30	
Objective	• To collect data on stone formation and the degree of nephrocalcinosis in patients (birth to adult) with PH3 and relatively intact renal function • To explore the potential relationship between Uox and new stone formation	
Duration of Participation	Follow-up every 6 months for up to 2 years	
Key Enrollment Criteria	*Inclusion* • Male or female (all ages) with genetically confirmed PH3 • History of stone events in the last 3 years and/or preexisting stones detected by ultrasound • At screening, 24-hr Uox ≥ 0.7 mmol OR average Uox-to-creatinine ratio > 95th percentile for age** • At screening, eGFR ≥ 30 mL/min/1.73 m^2 OR serum creatinine < 97th percentile of healthy population	*Exclusion* • Hepatic transplantation (prior or planned within study period) • Current or planned dialysis during study period
Key Endpoints	Uox excretion, rate of new stone formation, degree of nephrocalcinosis, quality of life	

Why is this study important?
PH3 is the most recently characterized subtype of PH. Long-term clinical progression of PH3 is not well understood. Recent evidence shows that patients with PH3 have recurrent stone activity persisting into adulthood, many of whom present with declining renal function. Exploration of the relationship between Uox and new stone formation will expand the knowledge of this subtype of PH.

**as defined by Matos et al. *Am J Kidney Dis.* 1999;34(2):e1.
Abbreviations: Uox: urinary oxalate; eGFR: estimated glomerular filtration rate

Figure 4: Enrolling Sites for PHYOX7, PHYOX8, and PHYOX-OBX

PHYOX7 sites
- Mayo Clinic, USA
- NYU School of Medicine, USA
- Boston Children's Hospital, USA
- Heidelberg University Hospital, Germany
- Hôpital Robert-debré, France
- Hôpital Femme Mère Enfant, France
- Hospital Universitario De Canarias, Spain
- Vall d'hebron Hospital, Spain
- Royal Free Hospital, UK
- Great Ormond Street Hospital, UK
- Ospedale Pediatrico Bambino Gesu, Italy
- Spitalul Clinic Municipal Dr. Gavril Curteanu Oradea, Romania
- Institutul Clinic Fundeni, Romania
- Kindernierenzentrum, Germany

PHYOX8 sites
- Mayo Clinic, USA
- Vall d'Hebron Hospital, Spain
- Great Ormond Street Hospital, UK

PHYOX-OBX sites
- The Hospital For Sick Children, Canada
- Hôpital Robert-debré, France
- Heidelberg University Hospital, Germany
- Hôtel-dieu de France Hospital, Lebanon
- Wojkowy Instytut Medyczny, Poland
- NYU School of Medicine, USA
- Boston Children's Hospital, USA
- Duke University Medical Center, USA

References

1. Cochat P, Rumsby G. Primary hyperoxaluria [published correction appears *in N Engl J Med.* 2013 Nov 28;369(22):2168]. *N Engl J Med.* 2013;369(7):649-658. doi:10.1056/NEJMra1301564
2. Garrelfs SF, Rumsby G, Peters-Sengers H, et al. Patients with primary hyperoxaluria type 2 have significant morbidity and require careful follow-up. *Kidney Int.* 2019;96(6):1389-1399. doi:10.1016/j.kint.2019.08.018
3. Martin-Higueras C, Garrelfs SF, Groothoff JW, et al. A report from the European Hyperoxaluria Consortium (OxalEurope) Registry on a large cohort of patients with primary hyperoxaluria type 3. *Kidney Int.* 2021;100(3):621-635. doi:10.1016/j.kint.2021.03.031
4. Singh P, Viehman JK, Mehta RA, et al. Clinical characterization of primary hyperoxaluria type 3 in comparison to types 1 and 2: a retrospective cohort study [published online ahead of print, 2021 Feb 5]. *Nephrol Dial Transplant.* 2021;gfab027. doi:10.1093/ndt/gfab027

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