PHYOX3: A Long-Term, Open-Label Extension Trial of Nedosiran in Patients with Primary Hyperoxaluria Type 1, 2, or 3

Bernd Hoppe[1], Martin Coenen[2], Gesa Schalk[2], Pierre Cochat[3], Graham Lipkin[4], John Lieske[5], Jaap W. Groothoff[6], Michelle A. Baum[7], Ralf Rosskamp[1]

[1]Dicerna Pharmaceuticals, Inc., Lexington, Massachusetts, United States; [2]University Hospital Bonn, Bonn, Germany; [3]Hôpital Universitaire Femme Mère Enfant, Lyon, France; [4]Queen Elizabeth Hospital, Birmingham, United Kingdom; [5]Mayo Clinic, Rochester, Minnesota, United States; [6]Emma Children's Hospital, Amsterdam UMC, Amsterdam, Netherlands; [7]Boston Children's Hospital, Boston, Massachusetts, United States

BACKGROUND

- Primary hyperoxaluria (PH) is a family of rare, autosomal recessive genetic disorders of hepatic glyoxylate metabolism that leads to overproduction of oxalate.
- Progressive renal damage results from the precipitation of calcium oxalate crystals in the kidney, causing recurrent stone formation and nephrocalcinosis that may culminate in renal failure.
- Nedosiran is an investigational ribonucleic acid interference (RNAi) therapy administered once monthly by subcutaneous injection.
- As a potential therapy, nedosiran is designed to reduce the overproduction of oxalate in the liver by targeting and decreasing the levels of hepatic lactate dehydrogenase A (LDHA) enzyme in patients with any of the three known genetic types of PH: PH1, PH2 or PH3.

OBJECTIVE

- The objective was to perform an interim analysis of the safety and efficacy data in patients with PH (PH1, PH2) who have completed the single-dose, open-label study PHYOX1 (NCT03392896) and have received monthly doses of nedosiran up to Day 180 in the ongoing, open-label PHYOX3 (NCT04042402) trial.

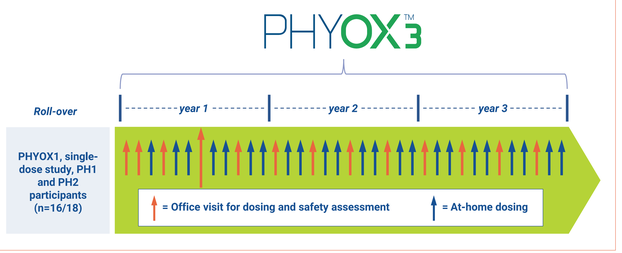
DESIGN

- PHYOX3 is designed to evaluate the long-term safety and efficacy of monthly nedosiran dosing in patients with genetically confirmed PH.

Criteria

- Male and female patients aged 6 years or more who have completed a previous nedosiran trial, and their siblings with genetically confirmed PH, are eligible for this trial
- Eligible participants must have a eGFR ≥ 30 mL/min normalized to 1.73 m^2 body surface area (BSA)
- Data presented here are from patients with PH1 or PH2 who completed PHYOX1 and elected to enroll in PHYOX3 (**Figure 1**)
  - N = 16 (demographics and safety): number of PHYOX1 participants enrolled in PHYOX3 and received nedosiran (170 mg) via subcutaneous injection
    - n = 13 (efficacy): participants who have reached the Day 180 timepoint
    - n = 3 participants have not yet reached the Day 180 timepoint

Figure 1. PHYOX3 Study Design



Efficacy

- 24-hour Uox excretion (absolute value, % change, maximum % reduction)
- Percentage of participants achieving NORMAL Uox excretion (< 0.46 mmol/24 hours) adjusted per 1.73 m^2 BSA
- Percentage of participants achieving NEAR-NORMAL (≥ 0.46 to < 0.60 mmol/24 hours) adjusted per 1.73 m^2 BSA. The NEAR-NORMAL analysis employed a strict and conservative threshold definition of 1.3x NORMAL

Safety

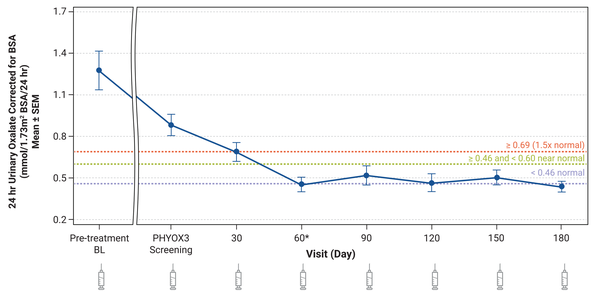
- Incidence and severity of treatment-emergent adverse events (TEAEs) and SAEs

RESULTS

Table 1. Demographics

Variable	PHYOX3
(n, %) unless specified	(N=16)
Age (years)	
Mean (SD)	25.9 (8.04)
Min, Max	14, 46
12-17 years	2 (12.5)
≥ 18 years	14 (87.5)
Gender	
Male:Female ratio	50:50
Race	
Asian	1 (6.3)
White	8 (50.0)
Not Applicable	7 (43.8)
Ethnicity	
Not Hispanic or Latino	12 (75.0)
Not Applicable	4 (25.0)
PHYOX3 Screening 24 hr Urinary Oxalate (mmol/1.73 m^2 BSA/24 hrs)	
Mean (SD)	0.920 (0.296)
Min, Max	0.523, 1.511
PH Type	
Type 1	13 (81.3)
Type 2	3 (18.8)
Time since PH Diagnosis (months)	
Mean (SD)	216.71 (92.507)
Min, Max	50.2, 475.9

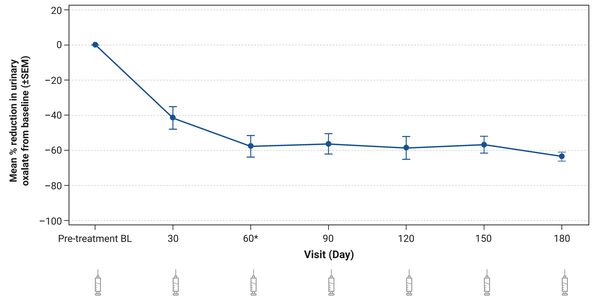
Figure 2. Absolute Change in Uox Excretion



*One participant was missing Uox value at Day 60.
The 1.5x NORMAL is included as an additional reference line.
Average Pre-treatment BL Uox excretion was 1.273 mmol/1.73 m^2 BSA/24 hours (mean of 2 screening values).

- Mean 24-hour Uox excretion for all participants at Day 180 was 0.44 mmol/1.73 m^2 BSA/24 hours

Figure 3. Mean Percentage Reduction in Uox Excretion From Pre-treatment Baseline



*One participant was missing Uox value at Day 60.

- Mean % reduction at Day 180 was 63.6% (range, 48.6% to 78.3%)
- The mean maximum reduction by Day 180 for all participants was 70.9% (range, 54.9% to 87.5%)
  - Mean maximum reduction for PH1 participants: 72.5% (range, 57.7% to 87.5%)
  - Mean maximum reduction for PH2 participants: 65.6% (range, 54.9% to 74.9%)

Table 2. Percentage of Participants Achieving Normalization and Near-Normalization of Uox Excretion by Day 180*

PH type	Normalization (n, %)	Normalization or Near-Normalization (n, %)
PH1 (n = 10)	10 (100)	10 (100)
PH2 (n = 3)	2 (67)	3 (100)
PH1 + PH2 (n = 13)	12 (92)	13 (100)

*Participants who achieved normal or near-normal values at one or more visits up to Day 180.

Table 3. Proportion of Participants Eligible to Decrease Hyperhydration & Discontinue Standard-of-Care Therapy

PH type	Eligible (n, %)
PH1 (n = 10)	7 (70)
PH2 (n = 3)	1 (33)
PH1 + PH2 (n = 13)	8 (62)

Participants achieving normal Uox excretion at 3 consecutive visits meet protocol-defined criteria to allow for decreasing hyperhydration and discontinuing standard-of-care therapy at the discretion of the investigator.

Table 4. PHYOX3 Interim Safety Data

Category	PHYOX3
Number of Subjects with at least one of the following:	(N=16)
TEAE (n, %)	16 (100.0)
TEAE occurring in ≥ 10% of patients in group	
Injection site pain	7 (43.8)
Injection site discomfort	6 (37.5)
Injection site erythema	5 (31.3)
Injection site discoloration	4 (25.0)
Injection site hematoma	3 (18.8)
Injection site atrophy	2 (12.5)
Flank pain	4 (25.0)
AST increased*	2 (12.5)
Headache	2 (12.5)
Nephrolithiasis	2 (12.5)
Pyrexia	2 (12.5)
TEAEs leading to discontinuation of study treatment	0
TEAEs leading to study withdrawal	0
Death	0
Serious TEAEs	2 (12.5)
Severity of TEAEs	
Mild	12 (75.0)
Moderate	2 (12.5)
Severe	2 (12.5)
ISR (protocol defined)	3 (18.8)

*Two participants had a TEAE AST increase reported but had elevated levels prior to receiving nedosiran therapy.
One participant (6.3%) had a TEAE ALT increase reported but had elevated levels prior to receiving nedosiran therapy.

- Majority of the TEAEs were mild to moderate in severity and related to administration site events
- No discontinuation of therapy, withdrawal from study, or deaths occurred during the observation period
- The two serious TEAEs (pyelonephritis and nephrolithiasis) were graded as severe and determined to be unrelated to nedosiran therapy, as these are considered common events in patients with PH
- Protocol defined injection site reactions (ISRs = signs or symptoms at the injection site with a time to onset of ≥ 4 hours from the time of nedosiran administration) occurred in less than 20% of participants

CONCLUSIONS

- All PH1 participants achieved normal Uox excretion at one or more timepoints by Day 180
- All PH2 participants achieved normal or near-normal Uox excretion at one or more timepoints by Day 180
- Nedosiran provided a durable treatment effect
  - 12 out of 13 participants achieved normal Uox excretion by Day 180
  - 1 out of 13 participants achieved near-normal Uox excretion by Day 180
  - 8 out of 13 participants met protocol-defined criteria to allow for decreased hyperhydration and other standard-of-care therapy
- Nedosiran was well tolerated and no serious safety concerns were identified in this patient population
  - Mild to moderate TEAEs
  - Majority were administration site related events

American Society of Nephrology, Kidney Week 2020, October 22-25, 2020.

Disclosures: The authors are investigators in the PHYOX3 trial. M. Baum: scientific advisory board - Dicerna, Retrophin, speaker - Alnylam; J. Lieske: Scientific advisory board - Dicerna, Alnylam, Allena, Novobiome, Orfan/Bridgebio, Synlogic, Oxidien, research grant - Dicerna, Alnylam, Allena, OxThera, Novobiome, Orfan/Bridgebio, Synlogic, Oxidien.
Study Funding: Trial funded by Dicerna Pharmaceuticals, Inc., Lexington, MA.