PHYOX2: Nedosiran Reduced Urinary Oxalate Excretion in Patients with Primary Hyperoxaluria

Michelle Baum[1], Craig Langman[2], Pierre Cochat[3], John Lieske[4], Shabbir Moochhala[5], Shuzo Hamamoto[6], Hiroyuki Satoh[7], Chebl Mourani[8], Gema Ariceta[9], Aniruddha Amrite[10], Bernd Hoppe[10,11]

[1]Boston Children's Hospital, Boston, MA, USA; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Hôpital Femme Mère Enfant, Lyon, France; [4]Mayo Clinic, Rochester, MN, USA; [5]Royal Free Hospital, London, UK; [6]Nagoya City University, Nagoya, Japan; [7]Tokyo Metropolitan Children's Hospital, Tokyo, Japan; [8]Hôtel Dieu de France, Beirut, Lebanon; [9]University Hospital Vall d'Hebron, Barcelona, Spain; [10]Dicerna Pharmaceuticals, Inc., Lexington, MA, USA; [11]University Hospital Bonn, Bonn, Germany

BACKGROUND

Primary hyperoxaluria (PH) is a family of three ultra-rare, autosomal recessive genetic disorders of hepatic glyoxylate metabolism (PH1, PH2, PH3). PH is characterized by endogenous overproduction of oxalate and subsequent hyperoxaluria, resulting in renal deposition of calcium oxalate as stones (nephrolithiasis) and/or as crystals in the parenchyma (nephrocalcinosis), often resulting in progressive kidney damage and kidney failure.

In patients with chronic kidney disease, an increase in plasma oxalate (Pox) can lead to calcium oxalate deposition in extrahepatic tissues in a process called systemic oxalosis. Oxalosis is mainly 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 within the PHYOX program. In this trial, when administered once monthly by subcutaneous injection, nedosiran reduced the overproduction of oxalate by reducing levels of hepatic lactate dehydrogenase enzyme (encoded by the *LDHA* gene).

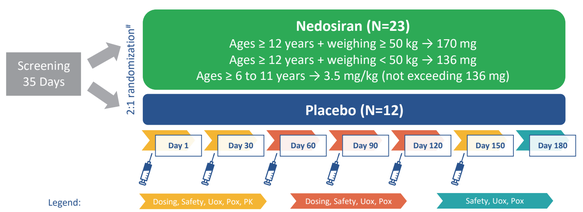
OBJECTIVE

- To report the results of the pivotal trial (PHYOX2) evaluating nedosiran in patients with PH1 and PH2

DESIGN

PHYOX2 (NCT03847909) is a pivotal, randomized, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of monthly nedosiran dosing in participants with primary hyperoxaluria (PH1 and PH2) over a 6-month treatment period [Figure 1].

Figure 1: PHYOX2 Trial Design



An adaptive randomization via minimization method was used to allocate participants to treatment groups with respect to age and eGFR. Nedosiran doses are expressed in terms of sodium salt.
Abbreviations: PK: Pharmacokinetics; Uox: Urinary oxalate; Pox: Plasma oxalate

Key Inclusion Criteria

- Male or female participants aged ≥ 6 years with genetically confirmed PH1 or PH2
- 24-hour Urinary oxalate (Uox) excretion ≥ 0.7 mmol (per 1.73 m^2 body surface area in age < 18 years)
- eGFR ≥ 30 mL/min/1.73 m^2 body surface area

Key Exclusion Criteria

- Prior renal or hepatic transplantation, or planned transplantation during trial period
- Current or planned dialysis during trial period
- Plasma oxalate > 30 µmol/L or documented evidence of clinical manifestations of systemic oxalosis

Study Objective

PHYOX2 tested whether nedosiran is superior to placebo in lowering Uox excretion over 6 months (Figure 2)

Figure 2: PHYOX2-Key Endpoints

Primary endpoint

Percent change from baseline in 24-hour Uox as measured by AUC from Day 90 to Day 180

Key Secondary endpoint

Proportion of participants reaching normalization or near-normalization of 24-hour Uox on at least 2 consecutive visits, starting at Day 90

Normalization = Uox < 0.46 mmol/24-hour; upper limit of assay-normal (ULN)
Near-Normalization = ≥0.46 to < 0.60 mmol/24-hour; 1.3 X ULN
Abbreviations: AUC: area under the curve

RESULTS

A total of 35 participants across 11 countries were enrolled in the trial (Table 1).

- Safety population and Intent-to-treat (ITT)* population: N=35 (23 nedosiran; 12 placebo)
- Modified ITT population (mITT)^: N=34 (22 nedosiran; 12 placebo)

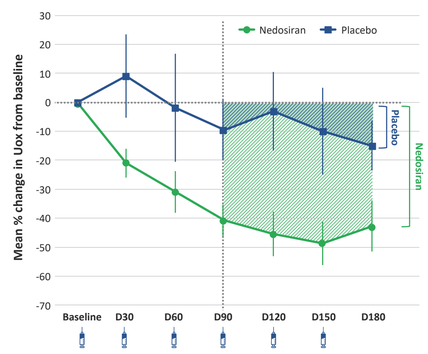
*Includes all participants who were randomized and had ≥ 1 post-baseline efficacy assessment; ^Includes all participants in the ITT population who had ≥ 1 efficacy assessment after Day 90

Table 1: PHYOX2 Demographics-Safety and ITT Population

Category	Nedosiran (n=23)	Placebo (n=12)
Age (years)		
Median (min, max)	20.0 (9, 46)	20.5 (10, 41)
6 – 11 years, n (%)	3 (13.0%)	2 (16.7%)
12 – 17 years, n (%)	6 (26.1%)	4 (33.3%)
≥ 18 years, n (%)	14 (60.9%)	6 (50.0%)
Gender		
Male: Female %	48:52	50:50
PH subtype, n (%)		
PH1	18 (78.3%)	11 (91.7%)
PH2	5 (21.7%)	1 (8.3%)
Baseline eGFR (mL/min/1.73 m^2)		
Mean (SD)	89.5 (37.5)	82.0 (30.0)
< 45 mL/min/1.73 m^2, n (%)	4 (17.4%)	1 (8.3%)
≥ 45 mL/min/1.73 m^2, n (%)	19 (82.6%)	11 (91.7%)
Baseline 24-hour Uox (mmol/day)		
Mean (SD)	1.33 (0.47)	1.96 (0.71)
Baseline Uox ≥ 1.6 mmol/day, n (%)	7 (30.4%)	10 (83.3%)
Baseline Plasma Oxalate (µmol/L), Mean (SD)	7.9 (5.1)	8.8 (5.1)
Years since PH diagnosis, Mean (SD)	7.1 (6.9)	7.4 (8.8)
Vitamin B6 intake	12 (52.2%)	9 (75.0%)

Abbreviations: BSA: body surface area; CKD: Chronic Kidney Disease; eGFR: estimated glomerular filtration rate.
Baseline 24-hour Uox is calculated as the average of the last two screening results prior to the first dose of study intervention. BSA adjusted 24-hour Uox values (mmol/24hr/1.73 m^2) are used for participants < 18 years old; eGFR < 45 mL/min/1.73 m^2 included CKD stage 3B and eGFR ≥ 45 mL/min/1.73 m^2 included CKD stages 1, 2, and 3A

Figure 3: Primary Endpoint: Standardized AUC of Uox from Day 90 to Day 180 (mITT Population)



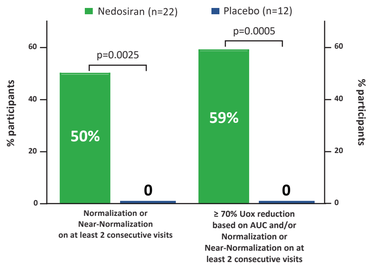
The observed % change in Uox from baseline between Day 90 and Day 180 (Figure 3 shaded area) was used to compute the standardized AUC, which signifies the integrated Uox exposure over 90 days (i.e., Day 90 to Day 180) instead of Uox change at any single timepoint (i.e., Day 90, 120, 150, or 180). The AUC is therefore a measure of the durability of Uox reduction over time.

% change in Uox based on actual observed values. Error bars represent ±SEM. D stands for Day

- PHYOX2 achieved the primary endpoint: Nedosiran showed a significantly greater (p<0.0001) reduction in Uox as measured by AUC from Day 90 to Day 180 compared to placebo[1] (Figure 3)
- A subgroup analysis in participants with baseline Uox ≥ 1.6 mmol/day (based on at least 1 value) also showed significantly greater Uox reduction in the nedosiran group (p=0.0186)

[1]Using an ANCOVA model with baseline age, Uox, and eGFR as covariates

Figure 4: Normalization or Near-Normalization of Uox Starting Day 90 (mITT Population)

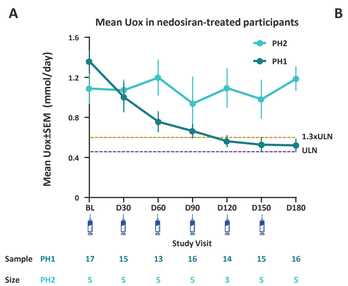


Normalization or Near-Normalization = < 1.3 x ULN (i.e., Uox < 0.6 mmol/day)

P value for one-sided test

- PHYOX2 met its key secondary endpoint (50% vs 0) [Figure 4]
- PHYOX2 also met a positive responder analysis (59% vs 0) [Figure 4]
- 16 out of the 22 participants (73%) treated with nedosiran achieved normalization (n=13) or near-normalization (n=3) at least once during the trial

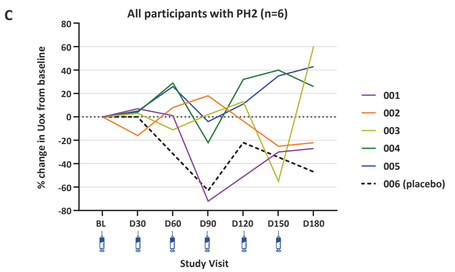
Figure 5: Subgroup Analysis in Nedosiran-Treated Participants with PH1 and PH2 (mITT Population)



B

Parameter	Nedosiran-PH1 (n=17)	Nedosiran-PH2 (n=5)
Normalized at any post-baseline visit through D180	65%	40%
Normalized or Near-normalized at any post-baseline visit through D180	82%	40%
Normalized at D180^	44%	0
Normalized or Near-normalized at D180^	81%	0

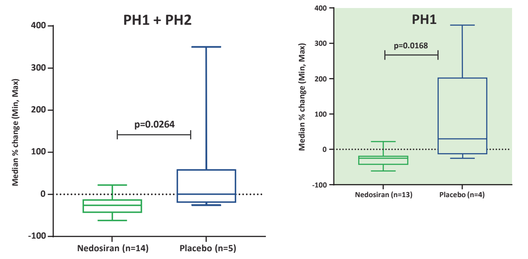
Normalization or Near-Normalization = < 1.3 x ULN (i.e., Uox < 0.6 mmol/day)



Abbreviation: BL, baseline
All percentages are based on the number of participants in the mITT Population with a non-missing value at specified visit; ^excludes 1 participant (PH1 cohort) that did not complete the trial

- The sustained Uox reduction observed in the trial was primarily seen in the nedosiran-treated participants with PH1 (Figures 5A and B)
  - Nedosiran-treated participants with PH1 achieved statistically significant differences from placebo for both the primary (p<0.0001) and the key secondary (p=0.0006) efficacy endpoints of the trial (post-hoc analysis)
- There was no consistent pattern of Uox reduction observed in the PH2 cohort (Figures 5A and C)

Figure 6: Percent Change in Plasma Oxalate from Baseline to Day 180 (ITT Population)



The boxes extend from the lower quartile (Q1) to upper quartile (Q3); the error bars represent the lowest and highest values. Post-screening plasma oxalate sampling was conducted only in adults (≥ 18 years old); missing values at Day 180 are not imputed; P value from a one-sided Wilcoxon Rank Sum Test

- Among the participants assessed for Pox, those treated with nedosiran showed a median decrease (25%) in Pox at Day 180, but overall not statistically significant (p=0.0264) compared to placebo (Figure 6)
  - Based on a post-hoc analysis, Pox reduction in the PH1 subgroup was statistically significant compared to placebo (Figure 6 inset in green)

Table 2: PHYOX2 Safety Data-Safety Population

Category	Nedosiran (n=23)	Placebo (n=12)
	Number (%) of participants	
AE occurring in ≥ 10% participants in either group		
• Injection site erythema	5 (21.7%)	0
• Headache	4 (17.4%)	3 (25.0%)
• Nausea	4 (17.4%)	1 (8.3%)
• Abdominal cramp	3 (13.0%)	2 (16.7%)
• Nephrolithiasis	2 (8.7%)	3 (25.0%)
• Renal colic	1 (4.3%)	2 (16.7%)
AE of special interest		
• Kidney stone events	3 (13.0%)	5 (41.7%)
• Injection site reaction*	2 (8.7%)	0
• Muscle pain or weakness	0	0
AE leading to discontinuation of treatment	1 (4.3%)	1 (8.3%)
SAE	1 (4.3%)	2 (16.7%)
Severe AE	1 (4.3%)	4 (33.3%)
Fatal AE	0	0

*: signs or symptoms at the injection site with a time to onset of ≥ 4 hours from the time of study drug administration

- 19 participants (82.6%) in the nedosiran group and 10 participants (83.3%) in the placebo group experienced at least 1 treatment-emergent adverse event (TEAE)
- The majority of TEAEs were mild or moderate in severity
- Injection site reactions occurred in < 10% of the participants in the nedosiran group and resolved by the end of trial
- No clinically important effects of nedosiran on laboratory or other clinical parameters were observed; there were no deaths in the trial

CONCLUSIONS

In this trial:

- Monthly administration of nedosiran lowered Uox burden in participants with PH1
  - Participants with PH1 treated with nedosiran showed a statistically significant and clinically meaningful reduction in Uox compared to those treated with placebo, with Uox being sustained in the normal or near-normal range
  - There was no consistent pattern of Uox reduction in the PH2 cohort, which suggests that oxalate production in PH2 is more complex than previously understood and warrants further investigation
- Nedosiran was generally safe and well tolerated in both the PH1 and PH2 cohorts
  - The majority of AEs were mild or moderate in severity
  - The AE profile of nedosiran is consistent with previously reported clinical data on nedosiran
  - No new risks were identified

DISCLOSURES

MB: Consultancy, Honoraria and Advisory board for Retrophin, Dicerna, Alnylam, Orfan, Chinook; Scientific advisor for OHF, ASN, Dent Disease Foundation; Research funding from Dicerna and Alnylam; **CL**: Consultant for Dicerna and Allena; **PC**: Advisory board for Alnylam, Dicerna, and Advicenne; **JL**: Consultant for Alnylam, Dicerna, OxThera, Allena, Siemens, ABIM, Orfan, Synlogic, Novobiome, Oxidien, Federation Bio; Research funding from OxThera, Retrophin, Allena, Siemens, Alnylam, Dicerna, Synlogic; Honoraria from ABIM and UpToDate; Scientific advisor/member of Kidney International, ABIM, OHF; **SM**: Honoraria from Shire, Sanofi; Scientific advisor for Dicerna, Alnylam, Allena; **SH**: Research funding from Takeda; Honoraria from Olympus, Johnson & Johnson, Ono Pharmaceutical; **HS**: Research funding from Dicerna; **CM** has nothing to disclose; **GA**: Consultancy and Honoraria from Astra Zeneca Alexion, Recordati, Chiesi, Kyowa Kirin, Advicenne; Consultant for Dicerna and Alnylam; Scientific advisor for Astra Zeneca Alexion; **AA** and **BH** are employees of Dicerna

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