PHYOX2

A Pivotal Randomized Study of Nedosiran in Primary Hyperoxaluria (PH) Type 1 or 2

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PHYOX2 was a Phase 2 pivotal, placebo-controlled, double-blind, 6-month efficacy, safety and tolerability study of nedosiran in patients with genetically confirmed PH1 and PH2.[1] ⊕

Eligibility Criteria[1]

Inclusion Criteria

Patients had to be ≥6 years of age with a 24-hour Uox excretion ≥0.7 mmol (adjusted per 1.73 m^2 BSA if <18 years of age) and an eGFR ≥30 mL/min per 1.73 m^2 BSA. Twelve or more patients were required to have ≥1 24-hour adjusted Uox excretion ≥1.6 mmol.

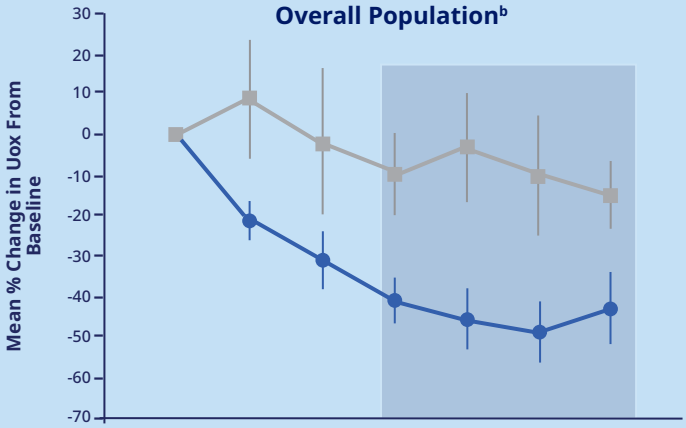
Exclusion Criteria

Patients with history of renal or liver transplantation, planned transplant, concurrent or planned dialysis or use of an RNAi drug within 6 months of the trial period were excluded.

Results[1]

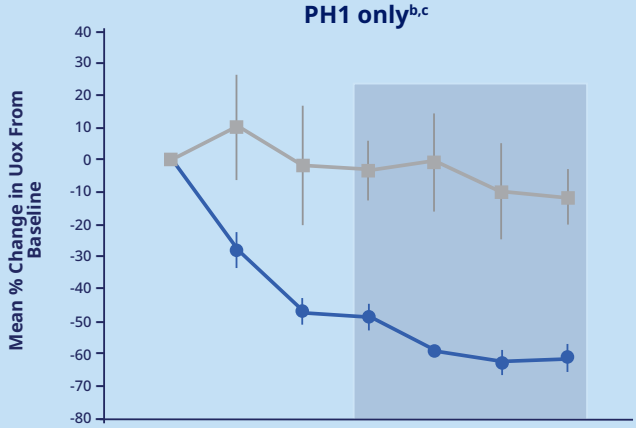
The **primary endpoint** was the 24-hour Uox excretion percent change from baseline as assessed by AUC between Day 90 and Day 180.[a]

Overall Population[b]



	LS mean (SE)
Nedosiran (N=22)	3507.4 (788.49)
Placebo (N=12)	-1664.4 (1189.96)
Difference (Nedosiran-Placebo)	5171.7 (1144.07), *P*<.001

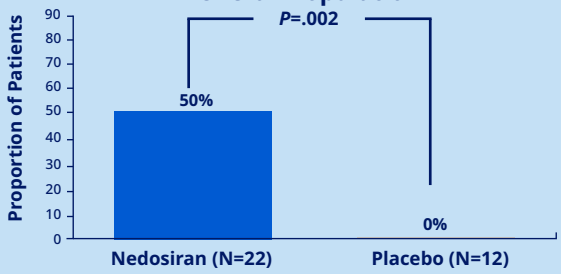
PH1 only[b,c]



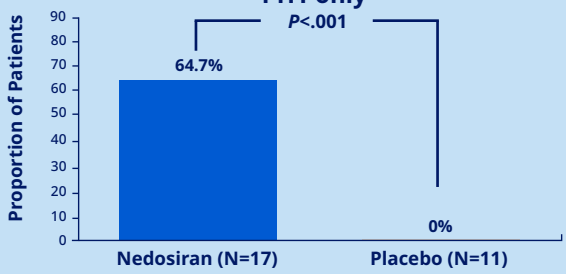
	LS mean (SE)
Nedosiran (N=17)	4571.1 (905.37)
Placebo (N=11)	-1316.7 (1284.81)
Difference (Nedosiran-Placebo)	5891.8 (1126.99), *P*<.001

The **key secondary endpoint** was proportion of patients reaching normal or near-normal 24-hour Uox excretion on 2 or more consecutive visits starting at Day 90.[d]

Overall Population



PH1 only[c]



[a]mITT population included all patients in the intent-to-treat population who had ≥1 efficacy assessment after Day 90
[b]Error bars represent +/- SEM
[c]PH1 subgroup analysis was prespecified for the primary endpoint and post-hoc for all other endpoints
[d]Patients had to meet the following 24-hour Uox excretion criteria on ≥2 consecutive visits beginning on Day 90: normal 24-hour Uox excretion (<0.46 mmol per 24 hours ULN) or near-normal (≥0.46 to < 0.60 mmol per 24 hours ULN or <1.3 times ULN)

Safety[1]

- TEAEs occurred in 19 (83%) patients in the nedosiran arm and 10 (83%) patients in the placebo arm (AE data include patients with PH1 and PH2). ⊕
- Majority of AEs were considered mild or moderate in severity.
- ISRs occurred in 2 (9%) patients in the nedosiran arm compared to 0 patients in the placebo arm. All ISRs were grade 1 and resolved by completion of the study.
- No participants in either group experienced muscle pain or weakness.

References: 1. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. *Kidney Int*. 2023;103(1):207-217.

Abbreviations: AE: adverse events; AUC: area under the curve; BSA: body surface area; eGFR: estimated glomerular filtration rate; ISR: injection site reaction; LS: least squares; mITT: modified intent-to-treat; N: number of patients; PH: primary hyperoxaluria; PH1: primary hyperoxaluria type 1; PH2: primary hyperoxaluria type 2; RNAi: ribonucleic acid interference; SE: standard error; SEM: standard error of mean; TEAEs: treatment-emergent adverse events; ULN: upper limit normal; Uox: urinary oxalate.