Long-Term Nedosiran Safety/Efficacy in PH1: 2.5-year Interim Analysis of PHYOX3

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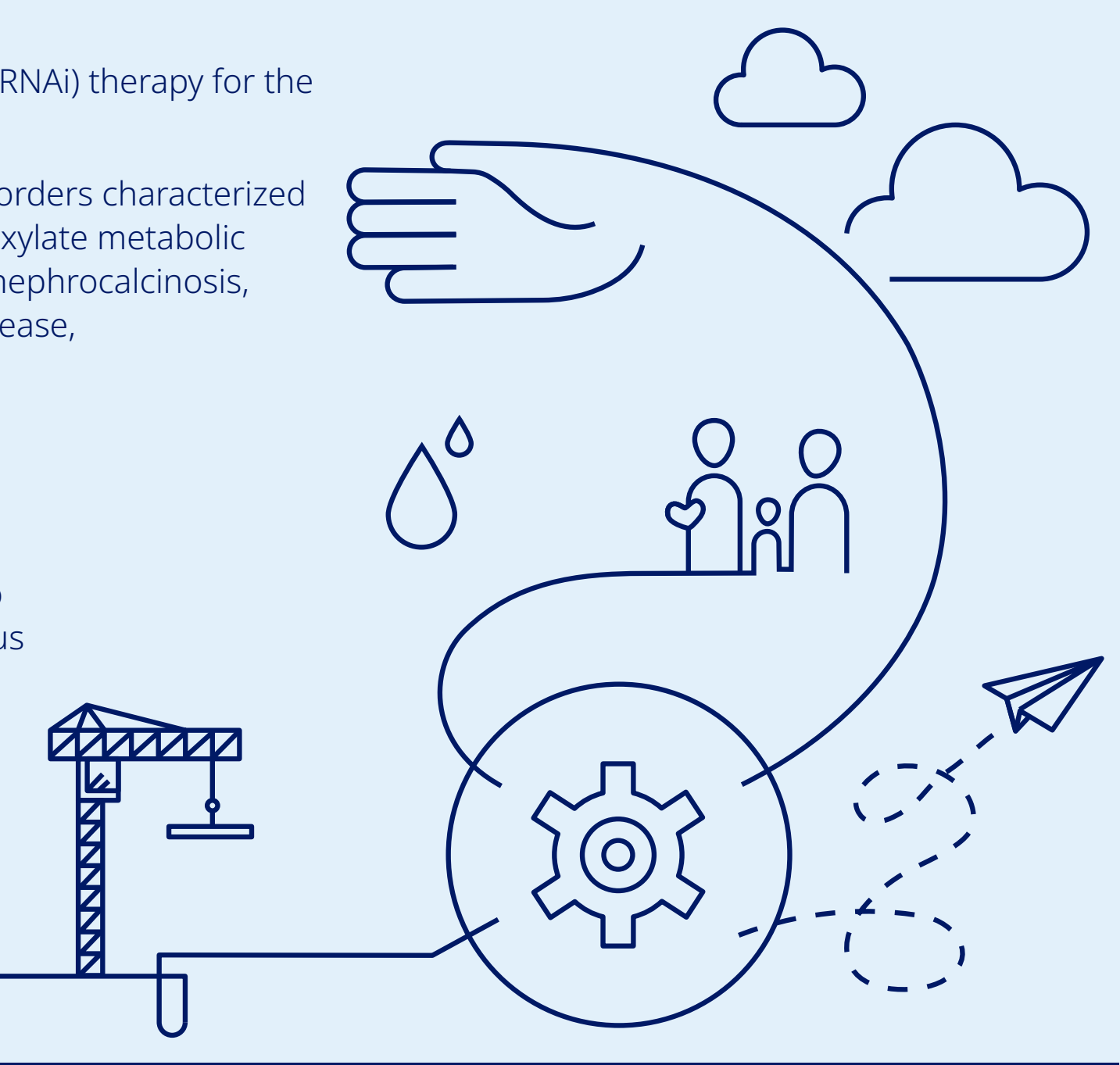
- Nedosiran is an FDA-approved RNA interference (RNAi) therapy for the treatment of primary hyperoxaluria type 1 (PH1)[1]
- PH is a family of three genetically distinct rare disorders characterized by deficiencies in the enzymes of the hepatic glyoxylate metabolic pathway resulting in urolithiasis, nephrolithiasis, nephrocalcinosis, progressive kidney damage, end-stage kidney disease, and systemic manifestations[2,3]
- In the PHYOX1 study population, nedosiran was generally well tolerated, had a favorable safety profile, and reduced urinary oxalate[2]
- In the PHYOX2 study population, nedosiran led to a significant and sustained reduction in Uox versus placebo and was well tolerated[2]
- The interim findings from the PHYOX3 study were consistent with those of the PHYOX1 and PHYOX2 trials[2]



Aim

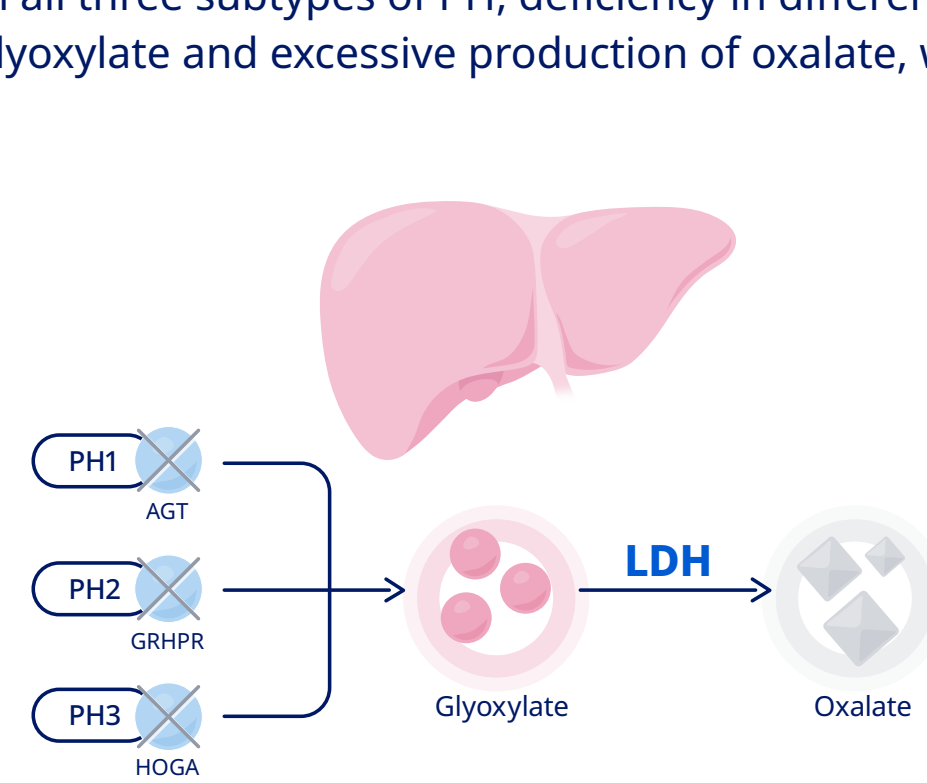
The interim analysis aims to evaluate the long-term safety and efficacy of monthly nedosiran in patients with PH1 who completed the PHYOX1 trial and continued to the PHYOX3 trial[2]

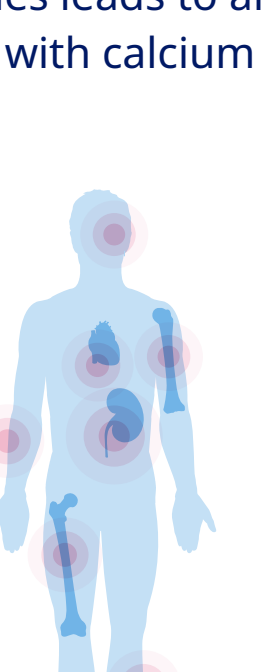
Contents

Primary hyperoxaluria (PH)
An overview

PH is a family of three genetically distinct, rare autosomal recessive disorders that lead to deficient enzymes of the hepatic glyoxylate metabolic pathway[2]

In all three subtypes of PH, deficiency in different hepatic enzymes leads to an abnormal increase in glyoxylate and excessive production of oxalate, which combines with calcium leading to kidney stones[2,3]





Manifestations of PH[2,3]

- Urolithiasis/Nephrolithiasis
- Nephrocalcinosis
- Progressive kidney damage
- Chronic kidney disease
- Systemic oxalosis

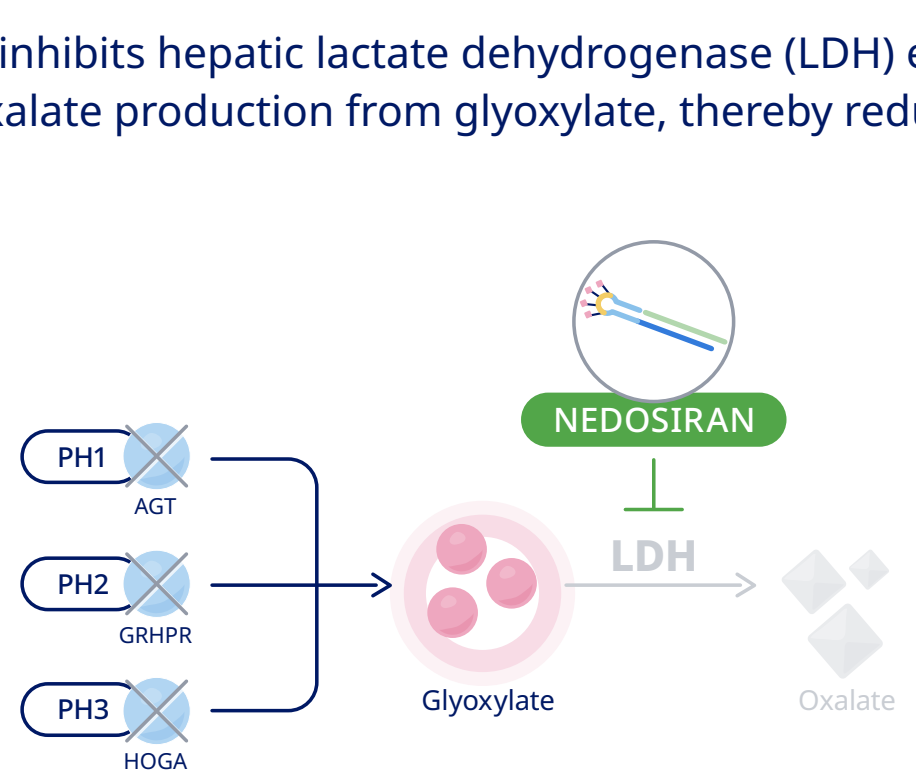
Conservative treatment options mostly consist of hyperhydration, vitamin B6 treatment for certain PH1 patients, and citrate medications[4]

Nedosiran
A new treatment for PH1

Nedosiran is an FDA-approved RNAi therapy for children ≥9 years old and adults with PH1 and relatively preserved kidney function[1]

- Approval was based on the PHYOX2 study population (i.e. patients ≥6 years old with PH1 or PH2 and an eGFR ≥ 30 mL/min/1.73 m²)[1]

It inhibits hepatic lactate dehydrogenase (LDH) expression, which is responsible for the final step in oxalate production from glyoxylate, thereby reducing the oxalate burden in PH1 patients[4]



- RNAi consists of small synthetic double-stranded RNA molecules that silence particular genes by interfering with translation and gene expression[5]
- Nedosiran silences the lactate dehydrogenase A (*LDHA*) gene which encodes for the hepatic LDH enzyme[6]
- In addition to nedosiran, lumasiran is also an FDA-approved RNAi treatment for PH1. It silences the hydroxyacid oxidase 1 (*HAO1*) gene, which encodes for the glycolate oxidase (*GO*) enzyme that converts glycolate to glyoxylate[7]

Study snapshots
PHYOX1 and PHYOX3

PHYOX1 (NCT03392896)[6,8]

A Phase 1, placebo-controlled, single-dose study of nedosiran in healthy volunteers and those with PH1 or PH2

PHYOX1 was a dose-finding safety and tolerability study[6,8]

Primary endpoint: To evaluate safety and tolerability of single ascending doses of nedosiran[6]

Treatment and dosing (Healthy volunteers) – Group A: Single-dose cohorts of sequentially higher-dose levels of subcutaneous (SC) nedosiran injections (0.3, 1.5, 3.0, 6.0, or 12 mg/kg) or placebo[6]

Treatment and dosing (Patients with PH1 or PH2) – Group B: Single dose of open-label SC nedosiran injections (1.5, 3.0, or 6.0 mg/kg)[6]

Key inclusion criteria for patients with PH1 or PH2:

- Genetically confirmed PH1 or PH2[6]
- Age ≥6 years[6]
- 24-hour Uox excretion ≥0.7 mmol for patients aged ≥18 years or ≥0.7 mmol/1.73 m² body surface area (BSA) for patients aged <18 years[6]
- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² BSA[6]

PHYOX3 (NCT04042402)[2]

An ongoing long-term Phase 3, open-label extension study of nedosiran in patients with PH1, PH2, or PH3

PHYOX3 is an open-label rollover study for participants that have successfully completed a previous nedosiran trial and their affected siblings[2]

Study aim: To evaluate the long-term safety and efficacy of monthly nedosiran[2]

Primary endpoint: Annual rate of decline in eGFR[2]

Treatment and dosing: Monthly nedosiran SC injection[2*]

- **Ages ≥12 years + weighing ≥50 kg:** 170 mg
- **Ages ≥12 years + weighing <50 kg:** 136 mg
- **Ages ≥6 to 11 years:** 3.5 mg/kg (not exceeding 136 mg)

Key inclusion criteria

- Successful completion of a nedosiran trial[2]
- 24-hour Uox excretion ≥0.7 mmol for patients aged ≥18 years or ≥0.7 mmol/1.73 m² BSA for patients aged <18 years[2]
- eGFR ≥30 mL/min/1.73 m² BSA[2]

Estimated enrollment:

- 75 participants[9]
- Participation will last approximately 6 years[9]

PHYOX3
Interim analysis population

The interim analysis only evaluates PHYOX1 PH1 completers who were aged ≥12 years (n=13)[2]

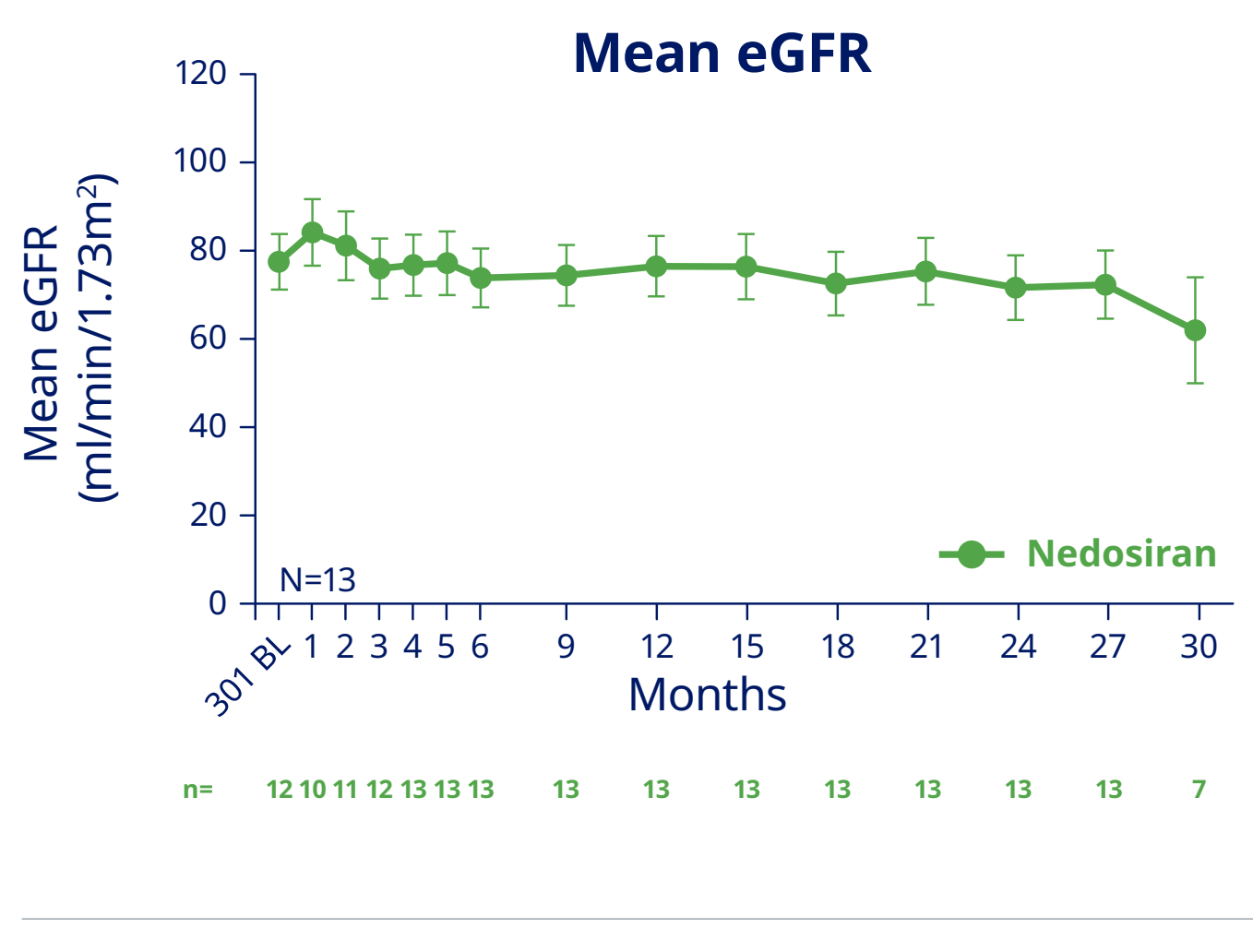
Participants received monthly nedosiran for 30 months[2]

There was a washout period of 10-23 months between PHYOX1 and PHYOX3[2]

Assessments include[2]:

- eGFR
- Safety and tolerability
- Uox burden
- Clinically apparent stone events and stone burden
- Eligibility for a reduction in original hyperhydration regimens or discontinuation of other co-medications

Primary endpoint
Annual rate of decline in estimated glomerular filtration (eGFR)

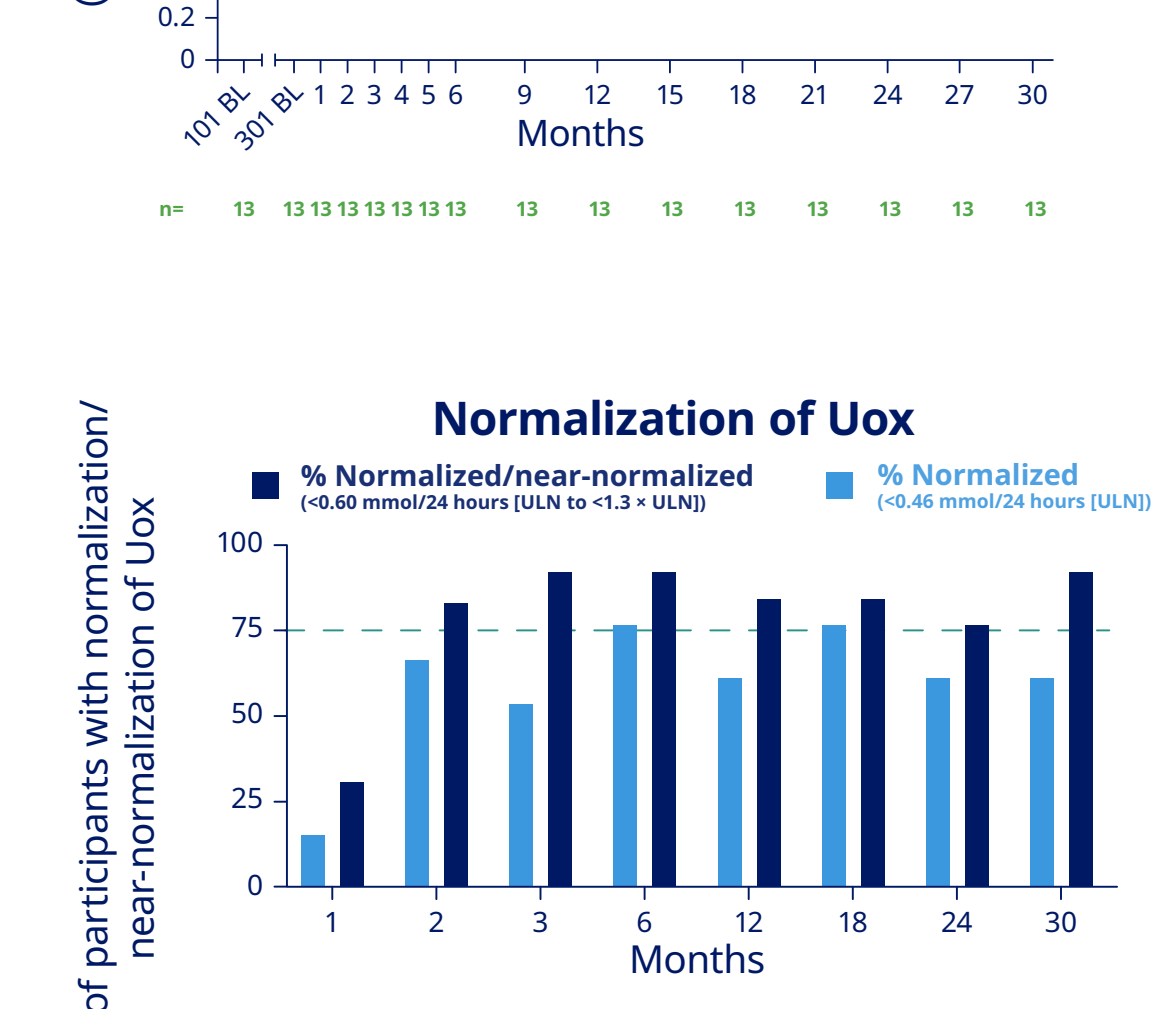


Mean eGFR remained stable (62–84.2 mL/min/1.73m²) from baseline to Month 30[2]

- Mean (SD) [range] eGFR at baseline was 75.5 (22.2) [36-114] mL/min/1.73 m²

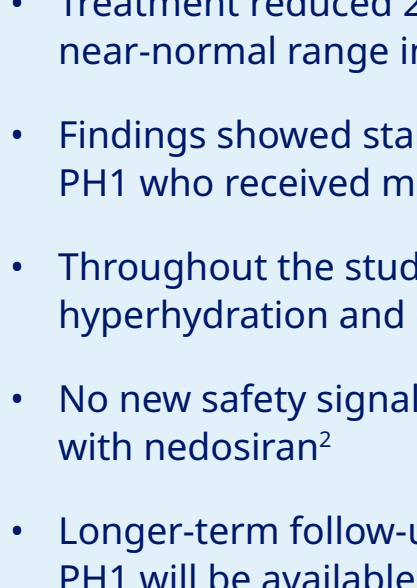
Secondary efficacy endpoint
Urinary oxalate (Uox) burden

- At baseline, patients had a mean Uox of 0.88 mmol/24 hours/1.73m². Robust reduction in Uox was seen starting at Month 2 which persisted through Month 30[2]
  - Most patients (at least 75%) experienced normal or near-normal Uox levels starting at Month 2 which persisted through Month 30[2]
- Eleven of 13 patients achieved normalized 24-hr Uox excretion at three consecutive timepoints, thus making them eligible for reduction of hyperhydration or discontinuation of co-medication[2]
- Based on post-treatment clinical data, the annualized stone event rate during the study period was 0.37 (5 [38.5%] participants, 12 events, 32.37 years exposed)[2]
  - All observed kidney stone events were considered mild or moderate in severity, and all events had recovered or resolved[2]
  - By comparison, the PHYOX2 placebo group (n = 11, mean [SD] baseline 24-hour Uox: 1.96 [0.71] mmol/d) had an annualized event rate during the study of 1.28 (4 participants [36.4%], 7 events, 5.49 years exposed)[2,10]

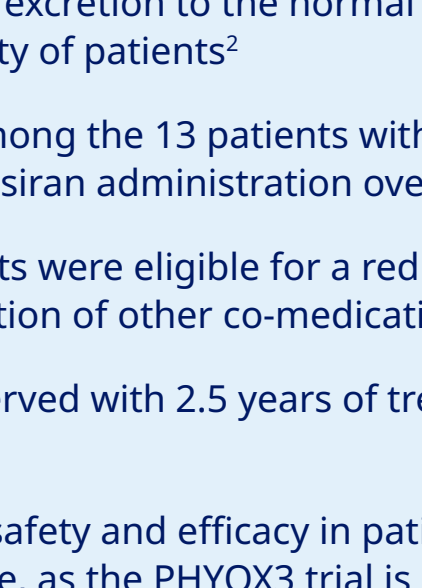


Secondary safety endpoint
Safety outcomes

Nedosiran was generally well tolerated, and injection site adverse events (AEs) were the most common treatment-related AE[2]



10 of 13 participants had treatment-related AEs[2]



3 of 13 participants had injection site reactions[2]

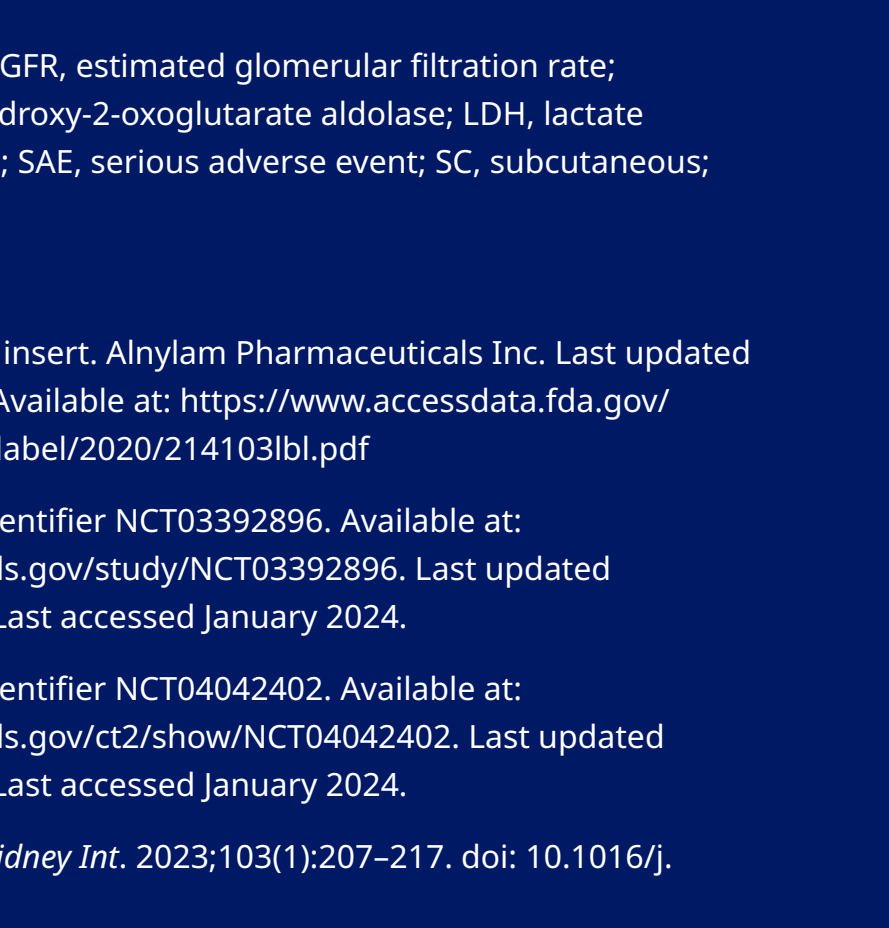
Most AEs were mild or moderate[2]

No serious treatment-related AEs[2†]

No study discontinuations due to AEs[2]

Key takeaways
The PHYOX3 interim analysis

- Nedosiran was well tolerated in patients with PH1, and treatment resulted in a sustained, substantial reduction in Uox excretion for at least 30 months in this long-term study[2]
- Treatment reduced 24-hour Uox excretion to the normal or near-normal range in the majority of patients[2]
- Findings showed stable eGFR among the 13 patients with PH1 who received monthly nedosiran administration over 2.5 years[2]
- Throughout the study, 11 patients were eligible for a reduction in hyperhydration and discontinuation of other co-medications[2]
- No new safety signals were observed with 2.5 years of treatment with nedosiran[2]
- Longer-term follow-up data for safety and efficacy in patients with PH1 will be available in the future, as the PHYOX3 trial is ongoing with a much larger patient cohort[2]



*The nedosiran dosage was based on weight as follows: adults and adolescents aged 12 to 17 years with weight ≥50 kg received 160 mg (1 ml volume, free acid; equivalent to 170 mg sodium salt); adults and adolescents weighing <50 kg received 128 mg (0.8 ml volume, free acid; equivalent to 136 mg sodium salt); and children aged 6 to 11 years (inclusive) were to receive 3.3 mg/kg (3.5 mg/kg sodium salt) not to exceed 128 mg.[2] †Three participants reported serious AEs. These SAEs were deemed not related to nedosiran.[2]

AE, adverse effect; AGT, alanine glyoxylate aminotransferase; BL, baseline; BSA, body surface area; eGFR, estimated glomerular filtration rate; GRHPR, glyoxylate reductase/hydroxypyruvate reductase; HAO1, hydroxyacid oxidase 1; HOGA, 4-hydroxy-2-oxoglutarate aldolase; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; PH, primary hyperoxaluria; RNAi, RNA interference; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse effect; ULN, upper limit of normal; Uox, urinary oxalate.

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