POSTER# C049

# Evaluating Efficacy and Safety of RNA Therapies Lumasiran and Nedosiran in Patients with Primary Hyperoxaluria Type 1 – a Systematic Literature Review

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## INTRODUCTION

- **Primary hyperoxaluria (PH)** includes three rare autosomal recessive disorders (PH1, PH2, PH3) caused by enzyme deficiencies in the hepatic glyoxylate metabolic pathway[1]
- **Primary hyperoxaluria type 1 (PH1)** results from a deficiency in alanine–glyoxylate aminotransferase, leading to excess oxalate production and elevated plasma oxalate levels[2]
- This excess can cause kidney stones, nephrocalcinosis and systemic oxalosis, affecting multiple organs[2]
- **Lumasiran**, introduced in 2020, is a ribonucleic acid (RNA) interference (RNAi) therapeutic that targets the *HAO1* gene, reducing glycolate oxidase production and decreasing oxalate formation[2]
- **Nedosiran** is an investigational RNAi therapeutic that degrades lactate dehydrogenase messenger RNA (mRNA), targeting hepatocyte uptake to reduce oxalate synthesis[3]
- Lumasiran and nedosiran are primary treatments for PH1, effectively addressing the disease's root cause and improving patient outcomes

## OBJECTIVES

- To identify and summarize the efficacy and safety of lumasiran and nedosiran therapies in patients with PH

## METHODS

- A systematic literature search was conducted on 23 May 2024, covering MEDLINE® and grey literature sources
- Eligible studies included patients with PH1, contained clinical data and were written in English
- The population, intervention, comparator, outcomes and study design (PICOS) criteria (Table 1) guided the identification of relevant studies
- Two reviewers independently screened titles and abstracts, which was followed by full-text assessments for eligibility
- Discrepancies were resolved through discussion or consultation with a third reviewer
- Data extraction and a methodological quality assessment were performed, and discrepancies were resolved by another independent reviewer

**Table 1. PICOS**

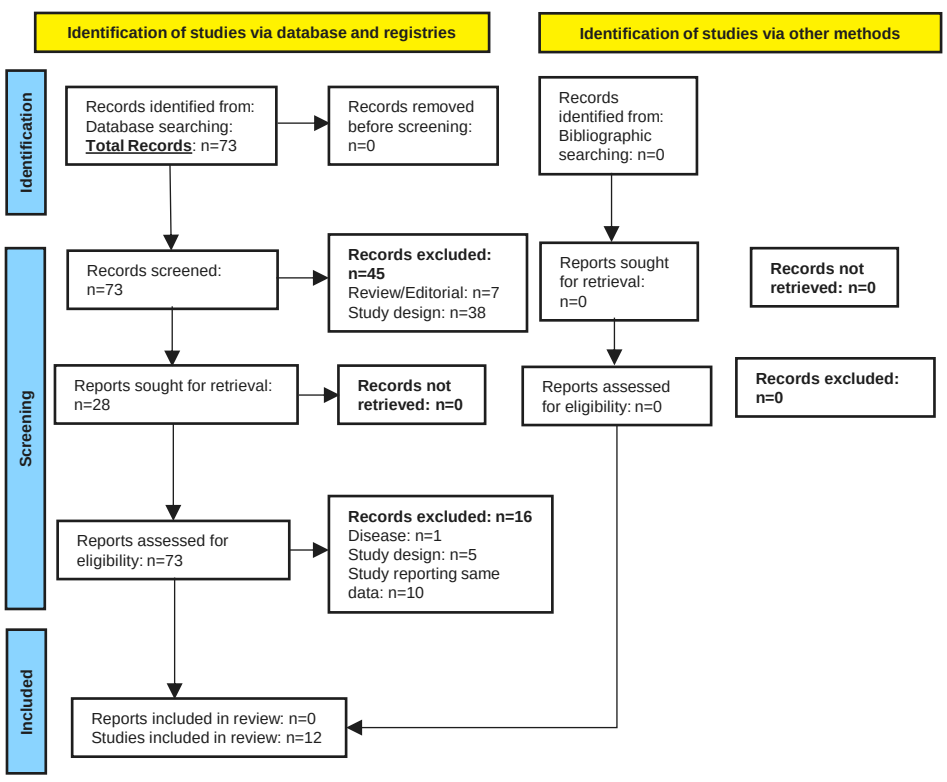
| Population | Intervention | Comparator | Outcomes | Study design | Time limit |
|---|---|---|---|---|---|
| Patients with PH1 disease | ▪ Lumasiran<br>▪ Nedosiran | No restrictions | ▪ Plasma oxalate levels<br>▪ Urinary oxalate levels<br>▪ Safety | ▪ RCTs<br>▪ Open-label extensions<br>▪ Single-arm trials | 2021–2024 |

**Key:** PH1, primary hyperoxaluria type 1; PICOS, population, intervention, comparator, outcomes and study design; RCT, randomized controlled trial.

## RESULTS

- An initial database search on 23 May 2024 identified 73 records; 45 were excluded after abstract screening, leaving 28 for full-text review
- Full-text screening excluded 16 records, leaving 12 eligible[1-12] for data extraction
- Ultimately, five clinical trials[1-3,9,11] spanning 12 publications[1-12] were included
- Among five clinical trials, four were randomized controlled trials[1-3,9] and one was an open-label extension[11]
- Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the systematic literature review

**Figure 1. PRISMA**




## Demographic details (Table 2)

- Patient ages ranged from mean (standard deviation [SD]) 9.7 (3.5)[13] to 26.5 (9.4)[3] years across all the trials. In ILLUMINATE-A[2], 30% were female and 70% were male. ALN-GO1-001[9] had a higher female proportion. PHYOX1[3] had equal gender distribution
- Estimated glomerular filtration rate (eGFR) levels ranged from a mean (SD) of 72.3 (18.2)[3] to 106.3 (23.5)[3] ml/min across all studies
- 24-hour urinary oxalate (UOx) excretion ranged from a mean (SD) of 1.3 (0.4)[1] to 1.8 (0.6)[2] mmol, and plasma oxalate levels ranged from 4.6 (4.2–4.9)[9] to 14.8 (7.6)[2] µmol

**Table 2. Baseline characteristics**

| Variables | Lumasiran | | | | Nedosiran | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ILLUMINATE-A[2] 3 mg/kg | ALN-GO1-001[9] 1 mg/kg | ALN-GO1-001[9] 3 mg/kg (qM) | ALN-GO1-001[9] 3 mg/kg (q3M) | PHYOX1[3] 1.5 mg/kg | PHYOX1[3] 3 mg/kg | PHYOX1[3] 6 mg/kg | PHYOX2[1] 170 mg/mL | PHYOX3[11]# |
| Patients | 26 | 7 | 7 | 3 | 6 | 8 | 4 | 23 | 13 |
| Age, n (%) | 18.7 (11.5) | 14 (9.9) | 15.4 (7.9) | 9.7 (5.51) | 26.5 (9.4) | 25.4 (6.7) | 16.5 (3.5) | 23.7 (11.9) | 24.2 (6.6) |
| Female, n (%) | 8 (30) | 6 (85.7) | 4 (57.1) | 2 (66.7) | 3 (50) | 4 (50) | 2 (50) | 12 (52.2) | 7 (53.8) |
| Male, n (%) | 18 (70) | 1 (14.3) | 3 (42.9) | 1 (33.3) | 3 (50) | 4 (50) | 2 (50) | 11 (47.8) | 6 (46.2) |
| eGFR (mL/min)α | 82.96 (25.5) | 81 (52.6-114.3)* | 75 (60.6-97.8)* | 99 (73.7-130.7)* | 72.31 (18.2) | 77.45 (28.1) | 106.34 (23.5) | 89.5 (37.5) | 75.5 (22.2) |
| 24h UOx excretionα | 1.84 (0.6) | 1.67 (0.9-2.9)* | 1.78 (0.8-2.7)* | 1.3 (0.9-1.7)* | NR | NR | NR | 1.3 (0.4) | 1.34 |
| Plasma oxalateα | 14.8 (7.6) | 7.7 (1.6-15.8)* | 9.1 (6.4-12.4)* | 4.6 (4.2-4.9)* | NR | NR | NR | 7.9 (5.1) | NR |

**Key**; eGFR, estimated glomerular filtration rate; qM, once per month; q3M, once every quarter; SD, standard deviation; UOx, urinary oxalate.
**Note**: *, Mean (range); α, Mean (SD); #Nedosiran dosage was weight-based: adults/adolescents ≥ 50 kg received 160 mg – those < 50 kg received 128 mg, and children aged 6–11 years received 3.3 mg/kg up to 128 mg.

## Efficacy data (Table 3)

**UOx excretion:**

- Lumasiran showed efficacy in reducing UOx excretion, achieving a 66.9% reduction in the ILLUMINATE-A trial.[2] In the ALN-GO1-001[9] trial, reductions ranged from 61.8% to 74%, depending on the dosage. Nedosiran produced a 50% reduction in UOx excretion in the PHYOX2 trial[1]

**Plasma oxalate levels:**

- Lumasiran led to a 36.9% decrease in plasma oxalate levels in the ILLUMINATE-A trial[2] and a reduction between 45.3% and 67% in the ALN-GO1-001 trial.[9] Nedosiran showed a 25% reduction in plasma oxalate levels in the PHYOX2 trial[1]

**Table 3. Efficacy outcomes**

| Trial name | Intervention | Timepoints | |
|---|---|---|---|
| | | Baseline | % reduction at 6 months |
| **24h UOx excretion (mmol/24h/1.73m²), mean (SE)** | | | |
| ILLUMINATE-A TRIAL/NCT03681184[2] | Lumasiran 3.0 mg/kg | 1.8 (0.60) | 66.9 (3.1) |
| ALN-GO1-001/NCT02706886[9] | Lumasiran 1.0 mg/kg | 1.9 (1.61-2.25) | 61.8 (15.2) |
| | Lumasiran 3.0 mg/kg qM | 1.6 (0.91-2.97) | 74 (11.2) |
| | Lumasiran 3.0 mg/kg q3M | 1.7 (0.83-2.76) | 63.2 (8.2) |
| PHYOX2/NCT03847909[1] | Nedosiran 170 mg/ml | 1.3 (0.47) | 50* |
| **Plasma oxalate level (µmol/l), mean (SE)** | | | |
| ILLUMINATE-A TRIAL/NCT03681184[2] | Lumasiran 3.0 mg/kg | 14.8 (7.6) | 36.9 (4.9)* |
| ALN-GO1-001/NCT02706886[9] | Lumasiran 1.0 mg/kg | 15.6 (10.7-20.5) | 45.3 (11.1) |
| | Lumasiran 3.0 mg/kg qM | 7.7 (1.6-15.8) | 73.4 (10.3) |
| | Lumasiran 3.0 mg/kg q3M | 9.1 (6.4-12.4) | 67 (0.5) |
| PHYOX2/NCT03847909[1] | Nedosiran 170 mg/ml | 7.9 (5.11) | 25 (61.9-22.2) |

**Key:** qM, once per month; q3M, once every quarter; SE, standard error; UOx, urinary oxalate.
**Note:** *Data reported to be statistically significant; 24h UOx excretion data reported at 3 months in PHYOX2 trial.

## Adverse event data (Table 4)

- Serious TEAEs were documented for both Lumasiran and Nedosiran, with rates varying from zero (0%) patients receiving Lumasiran and Nedosiran to three (38%) patients receiving Lumasiran and two (50%) patients receiving Nedosiran
- Common specific adverse events reported were injection-site reactions (0–11 [42%] patients), abdominal pain (0–3 [38%] patients), headache (0–2 [25%] patients) and rhinitis (0–3 [38%] patients)

**Table 4. List of adverse events**

| Adverse events | Lumasiran | | | | Nedosiran | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ILLUMINATE-A[2] 3 mg/kg | ALN-GO1-001[9] 1 mg/kg | ALN-GO1-001[9] 3 mg/kg qM | ALN-GO1-001[9] 3 mg/kg q3M | PHYOX1[3] 1.5 mg/kg | PHYOX1[3] 3 mg/kg | PHYOX1[3] 6 mg/kg | PHYOX2[1] 170 mg/mL | PHYOX3[11]# |
| Number of patients | 26 | 8 | 8 | 4 | 6 | 8 | 4 | 23 | 13 |
| TEAE, n (%) | 24 (92) | 8 (100) | 7 (87.5) | 4 (100) | 5 (83.3) | 8 (100) | 4 (100) | 19 (83) | 10 (76.9) |
| Serious TEAE, n (%) | 5 (19.2) | 1 (13) | 3 (38) | 0 | 0 | 2 (25) | 2 (50) | 1 (4.3) | 3 (23.1) |
| **Adverse events occurring in ≥ 10% of patients** | | | | | | | | | |
| Injection-site reactions, n (%) | 11 (42) | 1 (13) | 2 (25) | 0 | 1 (16.7) | 0 | 0 | 5 (22) | (82.7) |
| Abdominal pain, n (%) | 6 (23) | 1 (13) | 3 (38) | 1 (25) | 0 | 2 (25) | 1 (25) | 3 (13) | NR |
| Headache, n (%) | 4 (15) | 2 (25) | 2 (25) | 0 | NR | NR | NR | 4 (17) | NR |
| Rhinitis, n (%) | 2 (8) | 1 (13) | 3 (38) | 0 | 0 | 0 | 1 (25) | NR | NR |

**Key:** qM, once per month; q3M, once every quarter; TEAE, treatment-emergent adverse event.
**Note**: #Nedosiran dosage was weight-based: adults/adolescents ≥ 50 kg received 160 mg – those < 50 kg received 128 mg, and children aged 6–11 years received 3.3 mg/kg up to 128 mg.

## CONCLUSIONS

Lumasiran and nedosiran effectively lower UOx excretion and plasma oxalate levels in patients with PH1, improving renal outcomes over 6 months. Lumasiran shows sustained efficacy up to 36 months, while nedosiran also achieves significant oxalate reductions at 3 months, with many patients reaching normal levels. Both treatments maintain stable renal function. Most adverse events were mild, such as injection-site reactions and headaches, suggesting lumasiran's and nedosiran's potential as long-term therapies for PH1.

## References

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An electronic version of the poster can be viewed by scanning the QR code.

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