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Long-term Treatment with Lumasiran: Final Results from the Phase 2 Open-Label Extension Study

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INTRODUCTION

- PH1 is a rare genetic disorder in which overproduction of hepatic oxalate can lead to kidney failure and life-threatening systemic disease.[1-3]
- Lumasiran, an RNAi therapeutic indicated for treatment of PH1 to lower UOx and POx levels, reduces hepatic oxalate production by degrading the mRNA encoding glycolate oxidase.[4,5]
- Patients with PH1 who completed a Phase 1/2 study[6] (NCT02706886) were eligible to enroll in a Phase 2 OLE study (NCT03350451) within 12 months of completing the Phase 1/2 parent study.

METHOD

- Patients enrolled in the 54-month Phase 2 OLE study had previously met eligibility criteria for the Phase 1/2 parent study[6] (**Figure 1**).

Figure 1. Phase 2 OLE Study Design

PATIENT POPULATION (N=20)

- Enrollment within 12 months of completing Part B of the Phase 1/2 parent study[a]
  - Parent study eligibility criteria:
    - Age 6–64 years
    - Confirmed diagnosis of PH1[b]
    - eGFR >45 mL/min/1.73m^2
    - 24-hour oxalate excretion >0.7 mmol/24h/1.73m^2
    - Stable pyridoxine regimen

54-MONTH OPEN-LABEL EXTENSION LUMASIRAN DOSES/REGIMENS

qM or q3M (SC) dosing by weight[c]

- **Initial dosing was based on patient's dose/regimen in Part B of the Phase 1/2 parent study**
  - **1.0 mg/kg qM**
  - **3.0 mg/kg qM**
  - **3.0 mg/kg q3M**
- **Adjustments to doses/regimens were permitted to a maximum of 3.0 mg/kg qM**
- **All patients eventually transitioned to 3.0 mg/kg q3M (maintenance dose)**

[a]In Part B of the Phase 1/2 study in adults and children with PH1, single and multiple doses of lumasiran resulted in rapid and sustained suppression of UOx levels with an acceptable safety profile; duration of follow-up depended on the protocol version requirements at the time the patient underwent follow-up (range, 112–401 days).
[b]Diagnosis based on a documented genetic analysis, biochemical criteria, and the presence of AGXT gene variants or reduced hepatic AGT enzyme activity that was considered evidence of the disease state (medical history).
[c]Based on emerging safety, tolerability, and efficacy data from the Phase 1/2 study, all patients who received 1.0 mg/kg qM in Part B of the Phase 1/2 study were approved to transition to 3.0 mg/kg q3M in the Phase 2 OLE study.

- The primary endpoint was incidence of AEs, including kidney stone–related AEs.
  - Kidney stone–related AEs were identified by independent review of AE data by 3 Alnylam physicians, who met to obtain consensus for any discrepancies.
- Secondary endpoints included change over time in the following: 24-hour UOx corrected for BSA, 24-hour UOx:Cr, and eGFR.
- Exploratory endpoints included change over time in POx and plasma glycolate and incidence of ADAs.

RESULTS

Patients

- The Phase 2 OLE study enrolled all 20 patients (median age 11.5 years; 65% female) who completed the Phase 1/2 parent study.
- Most patients (65%) were taking pyridoxine (vitamin B6) at baseline (**Table 1**).

Table 1. Baseline[a] Characteristics

Characteristic	All Treated (N=20)
Age at screening, median (range), years	11.5 (6–43)
Female, n (%)	13 (65)
White race, n (%)	15 (75)
Pyridoxine (B6) use, n (%)	13 (65)
Genotype[b], n (%)	
PR/*	2 (10)
M/M or M/N	10 (50)
N/N	8 (40)
24-Hour UOx excretion corrected for BSA[c], median (range), mmol/24h/1.73m^2	N=19 2.20 (0.94–5.18)
24-Hour UOx:Cr, median (range), mmol/mmol	0.256 (0.113–0.561)
POx, median (range)[d], µmol/L	N=19 14.1 (6.3–28.7)
Plasma glycolate, median (range), µmol/L	N=17 146.0 (49–325)
eGFR[e], median (range), mL/min/1.73m^2	72.2 (42.5–130.7)

[a]Baseline data were derived from the Phase 1/2 parent study.
[b]PR was defined as NM_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile). M and N were defined based on Mandrile et al.[7] The asterisk (*) denotes any genotype of PR, M, or N. M, missense; N, nonsense; PR, pyridoxine-responsive.
[c]ULN=0.514 mmol/24h/1.73m^2 for 24-hour UOx corrected for BSA.
[d]ULN=12.11 µmol/L for POx, as determined based on data from 75 healthy adults.[8]
[e]eGFR was calculated based on the Modification of Diet in Renal Disease formula (age ≥18 years at enrollment) and the Schwartz Bedside Formula (age <18 years at enrollment).

- All patients transitioned to the 3.0 mg/kg q3M lumasiran dosing regimen by Month 21.
- All patients remained on study treatment through Month 45; 6 transitioned to commercially available lumasiran prior to Month 54.
- All patients completed the Phase 2 OLE study.

Safety

- Safety results are summarized in **Table 2**; the most common treatment-related AEs were ISRs, with 13 events affecting 8/20 patients (40%); all ISRs were mild in severity.
  - No ISRs were reported after Month 18 through the end of the study.
  - The kidney stone AE rate was low during the Phase 2 OLE study (0.17/PY).

Table 2. Safety

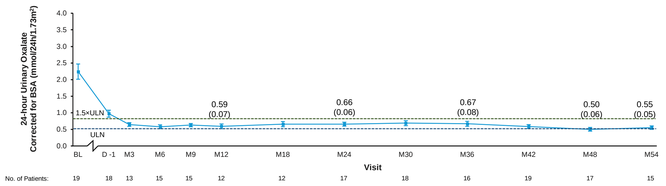
Category/Event	All Treated[a] (PY=80.5)
≥1 AE	20 (100) [227/282.1]
AEs reported by ≥3 patients	
COVID-19	9 (45) [9/11.2]
Injection site reaction	8 (40) [13/16.2]
Vomiting	6 (30) [9/11.2]
Headache	4 (20) [6/7.5]
Back pain	3 (15) [6/7.5]
Blood bilirubin increase	3 (15) [3/3.7]
Cough	3 (15) [6/7.5]
Limb injury	3 (15) [3/3.7]
Nasopharyngitis	3 (15) [3/3.7]
Nephrolithiasis	3 (15) [8/9.9]
Oropharyngeal pain	3 (15) [3/3.7]
Rhinitis	3 (15) [4/5.0]
SARS-CoV-2 test positive	3 (15) [3/3.7]
Ureterolithiasis	3 (15) [3/3.7]
Vitamin D deficiency	3 (15) [7/8.7]
≥1 Treatment-related AE[b]	11 (55) [21/26.1]
AEs leading to treatment discontinuation or study withdrawal	0 (0)
≥1 Severe AE[c]	2 (10) [4/5.0]
≥1 Serious AE[d]	7 (35) [13/16.2]
Death	0 (0)

[a]Data shown as N patients (%) [n events/exposure-adjusted rate per 100 PY]
[b]Treatment-related AEs included ISRs (n=8; 40%, all mild); blood bilirubin increase (n=3; 15%, 2 mild and 1 moderate); bilirubin conjugated increase (n=1; 5%, moderate); headache (n=1; 5%, moderate); electrocardiogram QRS complex prolonged (n=1; 5%, mild); and glycolic acid increased (n=1; 5%, mild).
[c]Severe AEs included tibia fracture, flank pain, nephrolithiasis, and ureterolithiasis (each n=1; 5%).
[d]Serious AEs included ureterolithiasis (n=3; 15%) and bone contusion, craniocerebral injury, glomerular filtration rate decrease, nephrolithiasis, pyelonephritis, renal colic, renal stone removal, thyroid mass, and thyroid operation (each n=1; 5%).

Urinary Oxalate

- Long-term lumasiran treatment led to a substantial reduction in mean 24-hour UOx relative to the Phase 1/2 parent study–derived baseline (**Figure 2**).

Figure 2. Mean (SEM) 24-Hour UOx Corrected for BSA Over Time



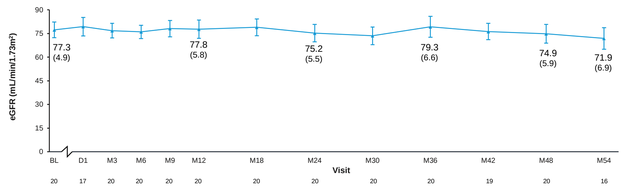
Dotted horizontal lines represent the ULN of 0.514 mmol/24h/1.73m^2 (1 mmol/24h/1.73m^2=90 mg/24h/1.73m^2) and 1.5× ULN (0.771 mmol/24h/1.73m^2) for 24-hour UOx excretion. Day −1 is the median of all measurements within 30 days of the first dose of lumasiran in the Phase 2 OLE study. Actual mean (SEM) UOx values at M12, M24, M36, M48, and M54 are shown in graph.

- At Month 54, the mean absolute change from baseline in 24-hour UOx was −1.5 mmol/24h/1.73m^2 and the mean percent change was −68%.
- Overall, 80% of patients (16/20) had normalization of 24-hour UOx (ie, at or below ULN of 0.514 mmol/24h/1.73m^2) at ≥1 post-baseline visit.
- In ≥89% of patients, 24-hour UOx was ≤1.5× ULN at visits Month 42 through Month 54.
- Measurements of 24-hour UOx:Cr over time were consistent with 24-hour UOx results.

eGFR

- Mean eGFR was generally stable over time (**Figure 3**); mean absolute change from baseline in eGFR through Month 54 ranged from −3.8 to 1.9 mL/min/1.73m^2.

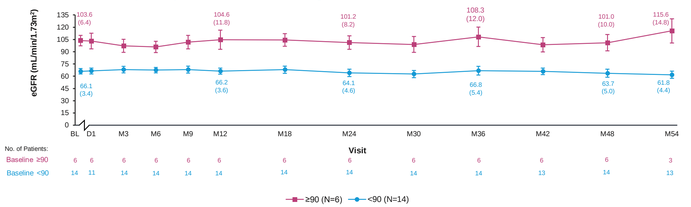
Figure 3. Mean (SEM) eGFR Over Time



eGFR was calculated based on the Modification of Diet in Renal Disease formula (age ≥18 years at enrollment) and the Schwartz Bedside Formula (age <18 years at enrollment). Baseline is the derived baseline value from the Phase 1/2 parent study. Actual mean (SEM) eGFR values at baseline, M12, M24, M36, M48, and M54 are shown in graph.

- Over 48 months of follow-up, the mean (SEM) annual eGFR rate of change for the 20 patients in the study was −0.6 (0.7) mL/min/1.73m^2.
- In one patient, who had one of the lowest eGFRs (51.7 mL/min/1.73m^2) and a kidney stone present at baseline, SAEs of eGFR decrease occurred during the study that were thought to be due to urinary tract obstruction from ureterolithiasis; these events were deemed unrelated to study drug by the investigator and the patient continued in the study.
- Stability of eGFR over time was consistent in a subgroup analysis by categorized eGFR at Phase 1/2 parent study–derived baseline (≥90 or <90 mL/min/1.73m^2; **Figure 4**).

Figure 4. Mean (SEM) eGFR Stratified by Baseline eGFR: ≥90/<90 mL/min/1.73m^2



eGFR was calculated based on the Modification of Diet in Renal Disease formula (age ≥18 years at enrollment) and the Schwartz Bedside Formula (age <18 years at enrollment). Baseline is the derived baseline value from the Phase 1/2 parent study. Actual mean (SEM) eGFR values at baseline, M12, M24, M36, M48, and M54 are shown in graph.

CONCLUSIONS

- In the longest reported follow-up to date (54 months), covering 80.5 patient years, lumasiran treatment was well tolerated and effective in patients with PH1.
- Mild ISRs, the most common treatment-related AEs, were infrequent, and none were reported after Month 18.
- Long-term lumasiran treatment led to sustained reductions in mean UOx to near-normal levels.
- eGFR was stable over time.

Secondary Endpoints

- Long-term lumasiran treatment also led to reductions from baseline in POx; mean post-baseline POx values remained within the normal range through Month 54.
- Mean plasma glycolate levels were elevated at the start of the Phase 2 OLE study due to persistence of the treatment effect from the Phase 1/2 parent study; after treatment resumed, levels increased and then plateaued, an effect consistent with the MOA of lumasiran.[4]
- One patient (5%) had a single ADA-positive result at Month 6 but had no ADA-related AEs; there was no impact on UOx response.

ABBREVIATIONS ADA, anti-drug antibody; AE, adverse event; AGT, alanine glyoxylate aminotransferase; BSA, body surface area; Cr, creatinine; eGFR, estimated glomerular filtration rate; ISR, injection site reaction; M, month; MOA, mechanism of action; mRNA, messenger RNA; OLE, open-label extension; PH1, primary hyperoxaluria type 1; POx, plasma oxalate; PY, patient-year; q3M, once every 3 months; qM, once monthly; RNAi, RNA interference; SAE, serious adverse event; SC, subcutaneous; ULN, upper limit of normal; UOx, urinary oxalate; UOx:Cr, urinary oxalate:creatinine ratio.

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