

13th Annual Conference on

NEPHROLOGY & RENAL CARE

May 24-25, 2018 Tokyo, Japan



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A phase 1/2 trial of Lumasiran, an investigational RNAi therapeutic for primary hyperoxaluria type-1

In Primary Hyperoxaluria type-1 (PH1), alanine-glyoxylate aminotransferase deficiency leads to excessive hepatic oxalate production, resulting in progressive renal impairment and multi-organ damage from systemic oxalosis. Lumasiran (ALN-GO1) is an investigational RNA Interference (RNAi) therapeutic which suppresses hepatic glycolate oxidase, decreasing the conversion of glycolate to glyoxylate, a required substrate for oxalate production. Data from healthy adult volunteers showed that single-dose Lumasiran was well tolerated with dose-dependent elevations in plasma glycolate. Here we report initial data from patients with PH1 in phase-2 of the ALN-GO1001 study. The phase-2 is a randomized, placebo controlled, single-blind, multicenter trial in patients with PH1 with urinary oxalate ≥ 0.7 mmol/24 hours/1.73 m² and eGFR >45 ml/min/1.73 m². One of four patients in each cohort is randomized to receive 3 doses of placebo prior to Lumasiran dosing. The first cohort received 1 mg/kg Lumasiran subcutaneously every 28 days $\times 3$ doses; the second cohort received 3 mg/kg Lumasiran. The primary endpoint is safety and secondary endpoints include change in 24 hours urinary oxalate from baseline. Lumasiran has demonstrated acceptable preliminary safety and tolerability with no treatment related serious adverse events or discontinuations from study. Initial results revealed all three patients randomized to Lumasiran in the first cohort experienced $>50\%$ decrease in urinary oxalate from baseline. The patient randomized to placebo was subsequently given Lumasiran 1 mg/kg monthly for three months and experienced similar reduction in urinary oxalate. All patients treated with Lumasiran experienced a lowering of urinary oxalate below 1.1 mmol/24 hours/1.73 m²; a threshold associated with reduced progression to end-stage renal disease. Data from the second cohort will be presented. Preliminary data show promising activity in lowering urinary oxalate in patients with PH1 and support development of Lumasiran as a potential therapeutic approach to alleviate pathologic overproduction of oxalate in this devastating disease.

Biography

Tracy McGregor has joined Alnylam Pharmaceuticals as the Director of Clinical Research in 2016 where she serves as the Medical Lead for the Lumasiran (formerly ALN-GO1) program. She has obtained her Medical degree at Washington University in St. Louis and her Master of Science in Clinical Investigation at Vanderbilt. Previously, she had worked in Vanderbilt University Medical Center as a Clinical Geneticist. She has trained in Pediatrics and Clinical Genetics at St. Louis Children's Hospital and holds board certification in both.

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