Lumasiran

An Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

Overview

- Lumasiran is an investigational, subcutaneously administered (under the skin) RNA interference (RNAi) therapeutic targeting hydroxyacid oxidase 1 (HAO1) in development for the treatment of primary hyperoxaluria type 1 (PH1). HAO1 encodes the glycolate oxidase (GO) enzyme.
- Lumasiran inhibits production of oxalate – the metabolite that directly contributes to the pathophysiology of PH1 – by silencing the *HAO1* gene and depleting the GO enzyme.
- PH1 is an ultra-rare, life-threatening disease in which a genetic defect in the liver causes oxalate overproduction.[1]
- Symptoms of PH1 are often associated with recurrent kidney stones and include flank pain, urinary tract infections, painful urination, and blood in the urine.[2,3]
- Progressive damage to the kidneys from oxalate buildup typically results in end-stage renal disease.[1,3]
- Patients with advanced disease require intensive dialysis often as a bridge to a dual kidney/liver transplant, which resolves the metabolic defect in the liver and replaces the damaged kidneys.[2,3]

Clinical Development

- The safety and efficacy of lumasiran are being evaluated in three global, multicenter Phase 3 clinical trials: ILLUMINATE-A, -B, and -C.
- **ILLUMINATE-A** (NCT03681184) is a randomized, double-blind, placebo-controlled Phase 3 study with an extended dosing period to evaluate the efficacy and safety of lumasiran in children and adults with PH1.
  - The primary endpoint is the percent change in 24-hour urinary oxalate excretion from baseline to Month 6.
  - Key secondary and exploratory endpoints in ILLUMINATE-A will evaluate additional measures of urinary oxalate, estimated glomerular filtration rate (eGFR), safety, and tolerability.
  - Topline results are expected in late 2019.

- **ILLUMINATE-B** (NCT03905694) is an open-label Phase 3 study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of lumasiran in infants and young children with PH1.
  - The primary endpoint is the percent change in urinary oxalate excretion from baseline to Month 6.
  - Key secondary and exploratory endpoints will evaluate additional measures of urinary and plasma oxalate, eGFR, safety, tolerability, and clinical outcomes.
  - Topline results are expected in mid-2020.

- **ILLUMINATE-C** (NCT04152200) is a single arm study to evaluate the efficacy, safety, PK, and PD of lumasiran in patients with advanced renal disease, including patients on dialysis.
  - The primary endpoint is the percent change in plasma oxalate from baseline to Month 6
  - Key secondary endpoints will evaluate additional measures of plasma oxalate and changes in: urinary oxalate, renal function, frequency and mode of dialysis, frequency of renal stone events, and measures of systemic oxalosis.
  - Topline results are expected in late 2020.

Regulatory Designations

- Breakthrough Therapy Designation by the U.S. Food and Drug Administration (FDA)
- Priority Medicines (PRIME) Designation from the European Medicines Agency (EMA)
- Orphan Drug Designations in both the U.S. and the European Union

For more information about lumasiran, please contact media@alnylam.com.

1. Cochat P and Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369:649-658.
2. Milliner DS et al. *GeneReviews®*; [updated Nov 30, 2017]. https://www.ncbi.nlm.nih.gov/books/NBK1283/.
3. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. *Kidney Int*. 2009, 75:1264-1271.