Hope for patients with primary hyperoxaluria type 1

Positive Phase 3 study met primary and all tested secondary endpoints with an encouraging safety profile for lumasiran, an investigational RNAi therapeutic.

PARMA, ITALY, June 7, 2020 /EINPresswire.com/ -- Primary hyperoxaluria type 1 (PH1) is an autosomal recessive inherited disorder that begins in childhood and adolescence. Various defects in the enzyme alanine-glyoxylate aminotransferase cause an overproduction of oxalate in the liver, which is excreted in the urine (hyperoxaluria). It leads to the formation of recurrent kidney stones, renal calcification (nephrocalcinosis) and kidney injury, even kidney failure; many such patients require dialysis even before they reach adulthood. It can be managed prophylactically by drinking large amounts of fluids (2-3 litres), but this is not tolerated by smaller children, especially. Hardly any effective therapies have been available so far. In some patients, the administration of vitamin B6 (pyridoxine) can reduce oxalate excretion. Another basic therapy is to administer alkali citrate, as this improves the solubility of oxalate in urine, but no currently available treatment addresses the cause of the disease.

Lumasiran, a subcutaneously administered investigational RNAi therapeutic, could close that gap. RNA interference (RNAi) is a natural biological gene silencing mechanism. Lumasiran silences the HAO1 gene that encodes the liver enzyme GO, thereby inhibiting hepatic production of oxalate – the metabolite that directly contributes to the clinical manifestations of PH1.

At the ERA-EDTA Congress today, the results of a randomized, double-blind, placebo-controlled Phase 3 study were presented. 39 patients (age≥6 years, 24hr urinary oxalate (UOx)≥0.70 mmol/24hr/1.73 m2, confirmed PH1 diagnosis, eGFR≥30 mL/min/1.73 m2) were randomized (2:1) and received either the investigational RNAi therapeutic or placebo once a month for 3 months followed by dosing once every 3 months. Lumasiran led to a statistically significant percent reduction in 24hr UOx excretion compared to placebo: the LS mean change from baseline after 6 months was -65.4% with lumasiran and -11.8% with placebo (LS mean difference: −53.5%; p=1.7×10−14). Lumasiran treatment also resulted in a majority of patients achieving near-normalization (84%) or normalization (52%) of urinary oxalate (versus 0% of those treated with placebo), and reductions in mean plasma oxalate relative to placebo. The most common adverse events related to lumasiran were injection-site reactions, all of which were mild and transient; no severe or serious adverse events were reported.

“Lumasiran resulted in rapid, sustained, and statistically significant reductions in urinary and

plasma oxalate levels and had an encouraging safety profile", concluded Sander Garrelfs from the Emma Children's Hospital, Amsterdam UMC, University of Amsterdam.

"We were very impressed by these results", added Maria Jose Soler Romeo, Chair of the Paper Selection Committee of the 2020 ERA-EDTA Congress. "It is now necessary to demonstrate that the drug not only reduces the overproduction of oxalate effectively, but can also prevent long-term injury to the kidneys. If that is the case, we will finally have a treatment for children and young people who are affected by this rare disease that prevents them from needing dialysis."

[1] Sander Garrelfs et al. ILLUMINATE-A, A PHASE 3 STUDY OF LUMASIRAN, AN INVESTIGATIONAL RNAI THERAPEUTIC, IN CHILDREN AND ADULTS WITH PRIMARY HYPEROXALURIA TYPE 1 (PH1). LBCT 4556, presented at the ERA-EDTA Congress 2020.

About ERA-EDTA
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