LB002

ILLUMINATE-A, A PHASE 3 STUDY OF LUMASIRAN, AN INVESTIGATIONAL RNAI THERAPEUTIC, IN CHILDREN AND ADULTS WITH PRIMARY HYPEROXALURIA TYPE 1 (PH1)

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Background and Aims:

PH1 is a rare genetic disorder characterized by hepatic oxalate overproduction, leading to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis. There are no approved pharmacologic therapies for PH1. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic that targets glycolate oxidase to reduce hepatic oxalate production. We report the first results from the six-month, double-blind period of ILLUMINATE-A, a randomized, placebo-controlled Phase 3 study to evaluate lumasiran in patients with PH1.

Method:

Key inclusion criteria: age$\geq$6 years, 24hr urinary oxalate (UOx)$\geq$0.70 mmol/24hr/1.73m^2, confirmed PH1 diagnosis, eGFR$\geq$30 mL/min/1.73m^2. Randomization: 2:1; lumasiran (n=26), placebo (n=13). Dosing: 3 mg/kg monthly$\times$3, then quarterly. Primary endpoint: percent change in 24hr UOx excretion from baseline to month (M) 6. Primary comparison: least square (LS) mean treatment difference in percent change from baseline (average of M3-6).

Results:

Lumasiran led to a statistically significant percent reduction in 24hr UOx excretion compared to placebo: the LS mean change from baseline to M6 (average of M3-6) was -65.4% with lumasiran and -11.8% with placebo (LS mean difference: -53.5%; $p=1.7 \times 10^{-14}$). Subgroup analyses of the primary endpoint showed a consistent effect of lumasiran across age, baseline UOx, eGFR, and concomitant pyridoxine use. Lumasiran led to statistically significant improvements in all hierarchically tested secondary endpoints, including: proportion of lumasiran-treated patients that achieved normalization or near-normalization of 24hr UOx at M6 (84% vs 0% of placebo-treated patients, $p=8.3 \times 10^{-7}$), and percent change in plasma oxalate from baseline to M6 (average of months 3-6) (-39.5%, $p=2.9 \times 10^{-8}$). There were no serious or severe adverse events. The most common adverse events related to lumasiran were mild, transient injection site reactions.

Conclusion:

Lumasiran resulted in clinically meaningful, rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels compared to placebo during the six-month double-blind period. Lumasiran has a favorable safety profile.