Efficacy and Safety of Lumasiran in Patients With Primary Hyperoxaluria Type 1: 24-Month Analysis of the ILLUMINATE-A Trial

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Objectives

The primary objective was to evaluate the efficacy and safety of lumasiran in patients with PH1 who were randomized to lumasiran during the ILLUMINATE-A study.

Methods

• Primary hyperoxaluria type 1 is a rare genetic disorder characterized by hepatic overproduction of oxalate.

• Excretion of excess oxalate by the kidney can result in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and ultimately kidney failure.

• Lumasiran is a subcutaneously administered, liver-directed RNAi therapeutic to lower UOx levels in patients with PH1.

• Lumasiran decreases hepatic oxalate production by inhibiting the production of GS
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Results

• Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and patients randomized to placebo received a maintenance dose of 3.0 mg/kg lumasiran at Months 6, 7, and 8.

• Patients initially randomized to placebo who crossed over to lumasiran after baseline at Month 24: 58.1% (Table 2).

• Mean eGFR remained stable in both groups during lumasiran treatment (Figure 5).

• The magnitude of 24-hour UOx reduction after 18 months of lumasiran treatment (24 months of lumasiran treatment) was similar to that at 12 months prior to consent to 0.80/person-year in the lumasiran/lumasiran group from Day 1 to Month 24 (Figure 6).

Conclusions

• Long-term lumasiran treatment resulted in sustained reductions in UOx and POx through 24 months of treatment in the lumasiran/lumasiran group (mean UOx reductions: 58.1%; mean POx reductions: 56.6%) and 18 months of treatment in the placebo/lumasiran group (UOs: 48.7%; POxs: 61.2%).

• Lower kidney stone event rates were observed after initiation of lumasiran, and event rates remained lower in the lumasiran/lumasiran group (historical: 3.19/person-year; 24 months of treatment: 0.80/person-year) and in the placebo/lumasiran group (historical: 0.54/person-year; 18 months of treatment: 0.28/person-year) through Month 24.

• Lumasiran demonstrated an acceptable safety profile in patients with PH1.

The most common AEs related to lumasiran were injection-site reactions, all of which were mild and transient.

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Safety Results:

• Overall total mean duration of lumasiran exposure was 21.2 months (range: 2.8–24.3) with 389 patients shown

• The majority of AEs were mild in severity.

• The most common related AEs were mild, transient injection-site reactions (Table 3).

• The most common injection site reactions of mild intensity were erythema, pain, pruritus, and swelling at the injection site were the most common injection site reactions (Table 3).

• Three patients had serious AEs, including abdominal pain (N=1), urosepsis (N=1), and a post-procedural complication (N=1); none were considered related to study drug (Table 2).

• There were no treatment interruptions or discontinuations related to lumasiran; no death occurred (Table 2).

Figure 1. Defect in PH1 Glycolate Oxidoreductase

Figure 2. ILLUMINATE-A Phase 3 Study Design

Figure 3. Percent Change in 24-Hour UOx During Lumasiran Treatment

Figure 4. Proportion of Patients With 24-Hour UOx ≤5.1 ≤ULN During Lumasiran Treatment

Figure 5. Mean eGFR Values During Lumasiran Treatment

Figure 6. Kidney Stone Event Ratesa

Table 1. ILLUMINATE-A: Baseline Characteristics

Table 2. Overview of Patients With PH1 During Lumasiran Treatment

Table 3. Safety Summary

Table 4. Changes in POx, UOx, and eGFR During Lumasiran Treatment