Lumasiran: Dosing Administration Window

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SUMMARY

- The recommended dosing regimen of lumasiran consists of monthly loading doses for 3 doses, followed by maintenance doses beginning 1 month after the last loading dose. Lumasiran is administered subcutaneously, and dosing is based on actual body weight.[1]
  - In the ILLUMINATE-A study, patients were randomized to receive either lumasiran or placebo loading doses once monthly for 3 doses, followed by maintenance doses every 3 months beginning 1 month after the last loading dose.[2,3] After receiving the first loading dose of lumasiran, the second and third loading doses as well as the first maintenance dose were administered within a ±4 day dosing window during 6-month double-blind treatment period for patients initially randomized to lumasiran and during the 3-month blinded treatment extension period for patients initially receiving placebo. In the OLE period, doses from Month 12 through the end of the study were to be administered within a ±28 day dosing window.[3]
  - In the ILLUMINATE-B study, patients received lumasiran once monthly for 3 doses at a dose based on body weight category, followed by maintenance doses once monthly (patients weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) beginning at Month 3.[4,5] The second loading dose at Month 1, the third loading dose at Month 2, and doses from Month 3 through Month 6 were to be administered within a ±14 day dosing window. During the 54-month extension period, doses were to be administered within a ±14 day dosing window for patients weighing <10 kg or within a ±28 day dosing window for patients weighing ≥10 kg.[5]
  - In the ILLUMINATE-C study, patients received lumasiran once monthly (±14 days) for 3 doses at a dose based on body weight category, followed by maintenance doses once monthly (patients weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) beginning at Month 3. Doses through Month 6 were to be administered within a ±14 day dosing window. Ongoing doses from Month 7 to the end of the study were to be administered once monthly (±14 days) in patients who weighed <10 kg or every 3 months (±28 days) in patients who weighed ≥10 kg.[6,7]

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CLINICAL DATA

ILLUMINATE-A

ILLUMINATE-A was a phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of lumasiran in adults and children ≥6 years old with PH1 and an eGFR ≥30 mL/min/1.73m^2. Patients were randomized (2:1) to receive subcutaneous injections of lumasiran 3 mg/kg (N=26) or placebo (N=13) once monthly for 3 loading doses, followed by maintenance doses once every 3 months beginning 1 month after the last loading dose. The primary endpoint was the percent change from baseline in 24-hour UOx excretion corrected for BSA at 6 months (average of visits from Month 3 through 6). After the 6-month double-blind treatment period, all patients received lumasiran in an optional 54-month OLE.[2] Of the 39 patients enrolled, 13 of the 13 in the placebo crossover arm and 24 of the 26 in the continuous lumasiran group completed treatment in the 54-month OLE.[8]

During the 6-month double-blind treatment period, patients were randomized (2:1) to receive loading doses of 3.0 mg/kg of lumasiran or placebo once monthly for 3 doses, followed by maintenance doses of 3.0 mg/kg of lumasiran every 3 months beginning 1 month after the last loading dose.[2,3]

For patients who received placebo during the double-blind period, a 3-month blinded treatment extension period enabled the transition to initiate lumasiran while investigators and patients remained blinded to the earlier double-blind period treatment assignment. For this reason, during the 3-month blinded treatment extension period, patients who had been randomized to lumasiran also received 2 monthly doses of placebo, so that all patients received blinded monthly treatment during this period (administered at the Month 6, 7, and 8 visits). At the Month 9 visit, all patients received their first open-label maintenance dose of lumasiran, marking the beginning of the OLE period, and lumasiran was administered every 3 months thereafter.[9]

After receiving the first loading dose of lumasiran, the second and third loading doses as well as the first maintenance dose were administered within a ±4 day dosing window during 6-month double-blind treatment period for patients initially randomized to lumasiran and during the 3-month blinded treatment extension period for patients initially receiving placebo. In the OLE period, doses from Month 12 through the end of the study were to be administered within a ±28 day dosing window.[3]

ILLUMINATE-B

ILLUMINATE-B (N=18) was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of lumasiran in infants and young children <6 years old with PH1 and an eGFR >45 mL/min/1.73m^2 (or normal serum creatinine for infants <12 months old). Patients received subcutaneous injections of lumasiran as determined by a body weight-based dosing regimen. The primary endpoint was the percent change from baseline in spot UOx:Cr at 6 months.[4]

During the 6-month treatment period, patients received loading doses of lumasiran once monthly for 3 doses at a dose based on body weight category, followed by maintenance doses once monthly (patients weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) beginning at Month 3. Doses of lumasiran were required to be administered at least 21 days apart.[4,5]

The second loading dose at Month 1, the third loading dose at Month 2, and doses from Month 3 through Month 6 were to be administered within a ±14 day dosing window. During the 54-month extension period, doses were to be administered within a ±14 day dosing window for patients weighing <10 kg or within a ±28 day dosing window for patients weighing ≥10 kg.[5]

ILLUMINATE-C

ILLUMINATE-C was a phase 3, open-label, single-arm study with a 6-month primary analysis period followed by an ongoing 54-month extension period to evaluate the efficacy, safety, pharmacokinetics, and

pharmacodynamics of lumasiran in full term infants to adult patients with advanced kidney disease with an eGFR ≤45 mL/min/1.73m^2 (or elevated serum creatinine if <12 months old) and POx ≥20 µmol/L. Patients enrolled in the study included those not receiving hemodialysis in Cohort A (N=6) and those receiving hemodialysis in Cohort B (N=15). Patients received subcutaneous injections of lumasiran as determined by a body weight-based dosing regimen. The primary endpoints were the percent change from baseline in POx at 6 months (Cohort A) and percent change from baseline in predialysis POx at 6 months (Cohort B).[6]

During the 6-month primary analysis period, patients received loading doses of lumasiran once monthly (±14 days) for 3 doses at a dose based on body weight category, followed by maintenance doses once monthly (patients weighing <10 kg) or once every 3 months (patients weighing ≥10 kg) beginning at Month 3. Doses through Month 6 were to be administered within a ±14 day dosing window. Ongoing doses from Month 7 to the end of the study were to be administered once monthly (±14 days) in patients who weighed <10 kg or every 3 months (±28 days) in patients who weighed ≥10 kg. Doses of lumasiran were required to be administered at least 21 days apart.[6,7]

OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[1]:

Recommended Dosage

The recommended dosing regimen of OXLUMO consists of loading doses (monthly for 3 doses) followed by maintenance doses (beginning 1 month after the last loading dose) administered subcutaneously as shown in Table 1.

Dosing is based on actual body weight.

Table 1. OXLUMO Weight-Based Dosing Regimen

Body Weight	***Loading Dose***	***Maintenance Dose (the maintenance dose should begin one month after the last loading does)***
Less than 10 kg	*6 mg/kg once monthly for 3 doses*	*3 mg/kg once monthly, beginning 1 month after the last loading dose*
10 kg to less than 20 kg	*6 mg/kg once monthly for 3 doses*	*6 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose*
20 kg and above	*3 mg/kg once monthly for 3 doses*	*3 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose*

Missed Dose

If a dose is delayed or missed, administer OXLUMO as soon as possible. Resume prescribed monthly or quarterly dosing, from the most recently administered dose.

ABBREVIATIONS

BSA = body surface area; eGFR = estimated glomerular filtration rate; OLE = open label extension; PH1 = primary hyperoxaluria type 1; POx = plasma oxalate; UOx = urinary oxalate; UOx:Cr = urinary oxalate:creatinine ratio.

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