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Lumasiran

Updated: January 6, 2023.

OVERVIEW

Introduction

Lumasiran is a synthetic small interfering RNA (siRNA) molecule directed against the mRNA of hydroxyacid oxidase 1 (HAO1) that is used to treat the rare genetic disease primary hyperoxaluria type 1. Lumasiran has not been linked to serum aminotransferase elevations during therapy or to instances of clinically apparent liver injury with symptoms or jaundice.

Background

Lumasiran (loo" ma sir' an) is a synthetic, double-stranded, small interfering RNA (siRNA) directed against the mRNA of hydroxyacid oxidase 1 (HAO1), an enzyme made in the liver that decreases the production of oxalate, a stable molecule that is not metabolized further and is excreted in the kidneys. Lumasiran was developed to treat primary hyperoxaluria type 1, a rare autosomal recessive disease marked by excessive production of oxalate due to a deficiency in the peroxisomal enzyme alanine-glyoxylate aminotransferase, which converts glyoxylate (the precursor of oxylate) to glycine. As a result, children with primary hyperoxaluria type 1 produce excessive oxalate in the liver which overwhelms the capacity of the kidney for excretion and results in formation of insoluble calcium oxalate crystals leading to nephrocalcinosis, recurrent kidney stones and progressive renal damage. With renal dysfunction, oxalate also accumulates in other organs causing damage to bone, skin, vascular endothelium, heart, eye and brain. The clinical manifestations of primary hyperoxaluria type 1 are variable but progressive renal failure is prominent and can lead to death in childhood or young adulthood. To facilitate its hepatic update, lumasiran is covalently linked to three N-acetylgalactosamine residues which bind to and are taken up by the hepatocyte-specific asialoglycoprotein receptor. Once taken up by cells, the siRNA is cleaved into smaller fragments and separated into single strands that bind and silence the mRNA of HAO1. In animal models, lumasiran reduced HAO1 mRNA levels in liver and oxalate accumulation in liver and kidneys. In placebo controlled trials of lumasiran in patients with hyperoxaluria, subcutaneous injections resulted in dose related reductions in serum and urinary oxalate levels. With 3 to 6 monthly injections of higher doses, oxalate levels fell by more than 50%. Lumasiran was approved for use in the United States in 2020 for children and adults with primary hyperoxaluria type 1. Lumasiran is available in solution in single dose prefilled syringes of 94.5 mg in 0.5 mL under the brand name Oxlumo. The recommended dose regimen varies by body weight. For patients weighing 20 kg or above, the dose is 3 mg/kg once monthly for 3 months followed by once every 3 months. Administration by a health care provider is recommended. Lumasiran is generally well tolerated but side effects can include injection site reactions, fatigue, arthralgias, diarrhea, abdominal pain, headache, and musculoskeletal pains. In preregistration studies, 5% to 13% of lumasiran treated patients developed anti-drug antibodies, but their presence was not associated with decreased efficacy or safety.

Hepatotoxicity

In multiple pivotal trials, lumasiran therapy was well tolerated and serum ALT elevations arose in less than 1% of patients that were invariably transient, mild-to-moderate in severity, and without accompanying symptoms or jaundice. In controlled trials, rates of ALT and AST elevations during lumasiran therapy were similar to those with placebo or comparator agents. Since its approval, there have been no published reports of liver injury attributed to lumasiran therapy. Thus, lumasiran is an unlikely cause of clinically apparent liver injury, although it still has had limited widescale clinical use.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The possible cause of hepatic injury from lumasiran or other siRNA therapeutics is not known. Lumasiran, like other siRNA therapeutic agents, is metabolized intracellularly by nucleases and is not a substrate of cytochrome P450 enzymes or hepatic transporters.

Outcome and Management

Lumasiran has not been linked to liver test abnormalities or to clinically apparent liver injury and regular monitoring of routine liver tests is not recommended.

Drug Class: Genetic Disorder Agents, siRNA and Antisense Agents

Other Therapeutic siRNA-based Agents: Givosiran, Inclisiran, Patisiran, Vutrisiran

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lumasiran – Oxlumo®

DRUG CLASS

Genetic Disorder Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Lumasiran	1834610-13-7	C530-H669-F10-N173-O320-P43-S6-Na43	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 06 January 2023

Abbreviations: HAO1, hydroxyacid oxidase 1; mRNA, messenger RNA; siRNA, small interfering RNA.

FDA. Lumasiran. Clinical Review. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214103Orig1s000IntegratedR.pdf

(The FDA clinical review of lumasiran for efficacy and safety reported from 57 patients, among whom there were no deaths or drug related serious adverse events, injection site reactions arising in 23% [vs none on placebo], ALT elevations arising in 16% [4/44] on lumasiran vs 15% [3/18] on placebo, all ALT elevations were less than 3 times ULN, transient, and not associated with symptoms or jaundice).

Setten RL, Rossi JJ, Han SP. The current state and future directions of RNAi-based therapeutics. Nat Rev Drug Discov. 2019;18:421–46. PubMed PMID: 30846871.

(Extensive review of gene silencing using RNA interference pathways and the potential of RNAi therapeutics which have promise in many genetic and acquired diseases including transthyretin amyloidosis [transthyretin], HIV infection [CCR5], HBV [HBV mRNA], alpha-1-antitrypsin deficiency [zz A1AT], hypercholesterolemia [PCSK9]).

Scott LJ, Keam SJ. Lumasiran: first approval. Drugs. 2021 Feb;81(2):277–282. PubMed PMID: 33405070.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of lumasiran shortly after its approval in the US mentions that adverse events of therapy were generally mild and transient, and there were no serious adverse events attributed to lumasiran and no discontinuations or deaths from adverse events).

Garrelfs SF, Frishberg Y, Hulton SA, Koren MJ, O'Riordan WD, Cochat P, Deschênes G, et al. ILLUMINATE-A Collaborators. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. N Engl J Med. 2021;384:1216–1226. PubMed PMID: 33789010.

(Among 39 patients with primary hyperoxaluria type 1 treated with lumasiran or placebo for 6 months, urine and serum oxalate levels decreased with lumasiran therapy and there were no serious adverse events and no clinically relevant changes in liver function tests).

Frishberg Y, Deschênes G, Groothoff JW, Hulton SA, Magen D, Harambat J, Van't Hoff WG, et al. study collaborators. Phase 1/2 study of lumasiran for treatment of primary hyperoxaluria type 1: a placebo-controlled randomized clinical trial. Clin J Am Soc Nephrol. 2021;16:1025–1036. PubMed PMID: 33985991.

(In early phase studies in 32 healthy controls and 20 adult and pediatric patients with primary hyperoxaluria type 1 treated with ascending doses of lumasiran or placebo, adverse events included injection site reactions [38% vs 0%], abdominal pain and headaches which were transient and mild, and there were no drug related serious adverse events or deaths, and no "clinically significant changes in laboratory measures" including liver function tests).

Hulton SA, Groothoff JW, Frishberg Y, Koren MJ, Overcash JS, Sellier-Leclerc AL, Shasha-Lavsky H, et al. Randomized clinical trial on the long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1. Kidney Int Rep. 2021;7:494–506. PubMed PMID: 35257062.

(Among 24 patients with primary hyperoxaluria type 1 maintained on lumasiran in an extension study of up to 24 months, improvements in oxalate plasma levels were maintained and nephrocalcinosis scores improved, while adverse events were generally mild [injection stie reactions in 41%, abdominal pain 18%, headaches in 10%] and there were "no clinically relevant changes in laboratory measures" [including liver function tests]).

Sas DJ, Magen D, Hayes W, Shasha-Lavsky H, Michael M, Schulte I, Sellier-Leclerc AL, et al. ILLUMINATE-B Workgroup. Phase 3 trial of lumasiran for primary hyperoxaluria type 1: A new RNAi therapeutic in infants and young children. Genet Med. 2022;24:654–662. PubMed PMID: 34906487.

(Among 18 children less than 6 years of age with primary hyperoxaluria treated with lumasiran for at least 6 months, plasma oxalate decreased by 32% and there were no serious adverse events and only mild injection site reactions [n=2], and "no clinically relevant changes in laboratory measures" including liver tests).

Michael M, Groothoff JW, Shasha-Lavsky H, Lieske JC, Frishberg Y, Simkova E, Sellier-Leclerc AL, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 ILLUMINATE-C trial. Am J Kidney Dis. 2022 Jul 14:S0272-6386(22)00771-5. Epub ahead of print.

(Among 21 patients with primary hyperoxaluria type 1 treated with lumasiran for at least 6 months, plasma oxalate levels fell by 33% to 42% while adverse events were largely mild and transient and included injection site reactions [24%], and there were no "clinically relevant trends" in laboratory measures including liver function tests).

Hayes W, Sas DJ, Magen D, Shasha-Lavsky H, Michael M, Sellier-Leclerc AL, Hogan J, et al. Efficacy and safety of lumasiran for infants and young children with primary hyperoxaluria type 1: 12-month analysis of the phase 3 ILLUMINATE-B trial. Pediatr Nephrol. 2022. doi: 10.1007/s00467-022-05684-1. Epub ahead of print.

(Further follow up of children with primary hyperoxaluria treated with lumasiran [Sas 2022] for 12 months, found further decreases in plasma oxalate levels [from -32% at 6 months to -47% at 12] and no new adverse events, injection site reactions reported in 3 children [17%] and "no clinically relevant changes in laboratory measures" including liver function tests).

Ranasinghe P, Addison ML, Dear JW, Webb DJ. Small interfering RNA: Discovery, pharmacology and clinical development–An introductory review. Br J Pharmacol. 2022 Oct 17. Epub ahead of print.

(Review of the history of development, mechanism of action, methods of delivery, clinical efficacy and safety of RNA silencing drugs including lumasiran, givosiran, inclisiran, patisiran and vutrisiran, discusses adverse events from lumasiran of injection site reactions, but does not mention hepatotoxicity or ALT elevations).

Sellier-Leclerc AL, Metry E, Clave S, Perrin P, Acquaviva-Bourdain C, Levi C, Crop M, et al. Isolated kidney transplantation under lumasiran therapy in primary hyperoxaluria type 1: a report of 5 cases. Nephrol Dial Transplant. 2022 Oct 28:gfac295. Epub ahead of print.

(Among 5 patients with primary hyperoxaluria type 1 and renal failure on hemodialysis who were treated with lumasiran for 5-17 months and the underwent renal transplantation, all survived and had no evidence of recurrence of oxalate renal injury; no mention of hepatotoxicity or ALT elevations).