Alnylam Announces Health Canada Authorization of OXLUMO™ (lumasiran), the First and Only Treatment for Primary Hyperoxaluria Type 1 to Lower Urinary Oxalate Levels in Paediatric and Adult Patients

Authorization Based on two Pivotal Phase III trials, ILLUMINATE-A and ILLUMINATE-B; Showing Significant Reduction in Urinary Oxalate which Drives the Progression of PH1 Disease

TORONTO, ON, May 18, 2022 - Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) is pleased to announce that Health Canada has issued a Notice of Compliance (NOC) authorizing OXLUMO™ (lumasiran) injection for subcutaneous use for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in paediatric and adult patients.[1]

PH1 is an ultra-rare and debilitating genetic disease of the liver characterized by oxalate overproduction.[2] Oxalate is an end-product of metabolism and high levels of it are toxic because it cannot be broken down by the human body. Oxalate overproduction results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones, nephrocalcinosis (renal deposition of calcium oxalate crystals), progression to ESKD (kidney failure), and systemic organ dysfunction.[3]

There are several types of primary hyperoxaluria (PH), however, PH1 is the most common and the most severe form accounting for 70 to 80 per cent of all PH cases.[4] PH1 affects approximately four individuals per million with some regions, such as the Middle East and North Africa having a higher genetic prevalence.[5] Symptom onset ranges from early infancy to sixty years of age with the median age being four to six years.[6] The remainder of affected cases present in adulthood with 20 to 50 per cent presenting late stages of chronic kidney disease when diagnosed.[7]

Until today, there were no authorized pharmaceutical therapies for PH1. The only curative treatment is a liver transplant and if the patient has already progressed to kidney failure, then a dual liver/kidney transplant is required. Unfortunately, liver transplantation is associated with high morbidity and mortality, and life-long immunosuppression, leaving patients with limited options.

“PH1 is a challenging condition to diagnose and treat due to significant variations in the age of onset, rate of disease progression, and associated clinical manifestations,” says Dr. Elizabeth Harvey, Pediatric Nephrologist, The Hospital for Sick Children (SickKids), Associate Professor Pediatrics, University of Toronto and member of Alnylam Canada’s Scientific Advisory Board. “The approval of this therapy presents patients with a novel treatment option that may potentially reduce the oxalate burden responsible for causing their disease.”

OXLUMO™ was granted NOC based on the results of a randomized, double-blind, placebo-controlled clinical study in patients six years and older with PH1 (ILLUMINATE-A) and in a

single-arm clinical study in patients less than 6 years of age with PH1 (ILLUMINATE-B).[8] The ILLUMINATE-A study showed that OXLUMO™ met its primary endpoint, evidenced by a 53 per cent mean reduction in urinary oxalate, and a 65 per cent mean reduction in urinary oxalate relative to baseline.[9] In ILLUMINATE-B, OXLUMO™ demonstrated a 72 per cent mean reduction in spot urinary oxalate:creatinine ratio from baseline to month six (averaged from months three to six), meeting its primary endpoint.[10]

"This milestone is exciting, as it represents the third RNAi treatment to be brought to Canada in 3 years to treat rare and ultra-rare diseases," says Colleen Coxson, Country General Manager, Canada, Alnylam Pharmaceuticals. "Unfortunately for many patients, it can often take years to diagnose a rare disease, and just as long to find a treatment. Bringing Oxlumo to Canadian patients with PH1 further cements Alnylam Canada's commitment to the rare disease community."

OXLUMO™ is a double-stranded siRNA that reduces the levels of the enzyme glycolate oxidase (GO) responsible for supporting the production of oxalate by targeting the hydroxy acid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in major cells of the liver known as hepatocytes through RNA interference. As a result, decreased GO enzyme levels reduce the amount of urinary and plasma oxalate levels, the underlying cause of disease manifestations in patients with PH1.[11]

"Previously there have been no authorized treatment options for PH1 in Canada, so this is a potentially life-changing milestone for people diagnosed with this debilitating disease – many of whom are infants and children. OXLUMO™ represents an exciting new frontier for the treatment of patients with this serious genetic disease," says Dr. Kristopher Garlick, Country Medical Director, Canada, Alnylam Pharmaceuticals.

About OXLUMO™ (lumasiran)

OXLUMO™ is a double-stranded iRNA therapeutic that reduces the levels of the enzyme glycolate oxidase (GO) by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production. This results in reduction of urinary and plasma oxalate levels, the underlying cause of disease manifestations in patients with PH1. As the GO enzyme is upstream of the alanine:glyoxylate aminotransferase (AGT) enzyme, the deficiency of which causes PH1, the mechanism of action of lumasiran is independent of the underlying AGXT gene mutation encoding AGT.[12] In the ILLUMINATE-A study, OXLUMO™ was shown to significantly reduce levels of urinary oxalate relative to placebo, with the majority of patients reaching normal or near-normal levels. Injection site reactions (ISRs) were the most common drug-related adverse reaction.[13] In the ILLUMINATE-B study, OXLUMO™ demonstrated an efficacy and safety profile consistent to that observed in ILLUMINATE-A.[14] OXLUMO™ is administered via subcutaneous injection once monthly for three months, then once quarterly thereafter at a dose based on actual body weight. For patients who weigh less than 10 kg, ongoing dosing remains monthly. OXLUMO™ should be administered by a healthcare professional.[15]

About Primary Hyperoxaluria Type 1 (PH1)

PH1 is an ultra-rare genetic disease that is characterized by oxalate overproduction in the liver, causing renal damage. Renal damage is caused by a combination of tubular toxicity from oxalate,

calcium oxalate deposition in the kidneys, and urinary obstruction by calcium oxalate stones. PH1 is associated with a progressive decline in kidney function, which exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and deposition of oxalate in bones, eyes, skin, and heart, leading to severe illness and death. Management options to date have been limited to hyperhydration, crystallization inhibitors and, in a minority of patients with a specific genotype, pyridoxine (vitamin B6). These measures only delay the inevitable progression to kidney failure and the need for intensive dialysis as a bridge to a dual or sequential liver/kidney transplant. Other impacts of the disease include: infants often fail to thrive, meaning they are weak and not growing or developing at a normal rate.[16] Affected children frequently face developmental challenges, with social barriers and the requirement of accommodations to be made at school to meet their special medical needs.[17]

About RNAi

RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.

About Alnylam Pharmaceuticals

Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a new class of innovative medicines with the potential to improve the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS) diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust discovery platform. Alnylam has a deep pipeline of investigational medicines, including five product candidates that are in Phase 3 clinical trials and one in registration. Looking forward, Alnylam will continue to execute on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Alnylam employs over 1,200 people worldwide and is headquartered in Cambridge, MA. Alnylam Canada is headquartered in Mississauga, Ontario with established operations since June 2018.

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