Alnylam Announces U.S. Food and Drug Administration Acceptance of Supplemental New Drug Application for OXLUMO® for the Treatment of Advanced Primary Hyperoxaluria Type 1

Mar 01, 2022

PDUFA Date Set for October 6, 2022

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 1, 2022-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52586745&newsitemid=20220301005123&lan=en-

US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=3ece10f972347e30baa7fddf8cd8d819) (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the U.S. Food and Drug Administration (FDA) has accepted the Company's supplemental New Drug Application (sNDA) for lumasiran, an investigational RNAi therapeutic targeting hydroxyacid oxidase 1 (HAO1) – the gene encoding glycolate oxidase (GO) – for the reduction of plasma oxalate in the treatment of patients with advanced primary hyperoxaluria type 1 (PH1). The FDA has set an action date of October 6, 2022, under the Prescription Drug User Fee Act (PDUFA).

"We are pleased that the FDA has accepted our sNDA for lumasiran based on the positive six-month results of the ILLUMINATE-C study showing that lumasiran can substantially reduce plasma oxalate levels in patients with compromised renal function due to PH1, including those on hemodialysis," said Pushkal Garg, MD., Chief Medical Officer and EVP, Clinical Development and Medical Affairs at Alnylam. "This filing acceptance is a positive step for patients with advanced PH1, who are at risk for the devastating complications of systemic oxalosis."

Additionally, a Type II Variation for lumasiran to amend the label to further inform on the use of lumasiran in patients with advanced PH1 was submitted to and validated by the European Medicines Agency (EMA) in December 2021. The application is undergoing review by the Committee for Medicinal Products for Human Use (CHMP), which will then issue an opinion to the European Commission.

In 2020, OXLUMO was approved by the FDA for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients and by the EMA for the treatment of PH1 in all age groups.

OXLUMO® (lumasiran) INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

OXLUMO is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.

Important Safety Information

Adverse Reactions

The most common adverse reaction that occurred in patients treated with OXLUMO was injection site reaction (38%). Symptoms included erythema, pain, pruritus, and swelling.

Pregnancy and Lactation

No data are available on the use of OXLUMO in pregnant women. No data are available on the presence of OXLUMO in human milk or its effects on breastfed infants or milk production. Consider the developmental and health benefits of breastfeeding along with the mother's

clinical need for OXLUMO and any potential adverse effects on the breastfed child from OXLUMO or the underlying maternal condition.

For additional information about OXLUMO, please see the full U.S. Prescribing Information (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com%2Foxlumo-us-prescribing-information&esheet=52586745&newsitemid=20220301005123&lan=en-US&anchor=Prescribing+Information&index=2&md5=ddefa8621725779eab2f9656440afae8).

About Lumasiran

Lumasiran is a subcutaneously administered RNAi therapeutic targeting hydroxyacid oxidase 1 (*HAO1*) in development for the treatment of advanced primary hyperoxaluria type 1 (PH1). *HAO1* encodes glycolate oxidase (GO). Thus, by silencing *HAO1* and depleting the GO enzyme, lumasiran inhibits production of oxalate – the metabolite that directly contributes to the pathophysiology of PH1. Lumasiran utilizes Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. Lumasiran has received regulatory approvals from the U.S. Food and Drug Administration (FDA) for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients and from the European Medicines Agency (EMA) for the treatment of PH1 in all age groups under the brand name OXLUMO®.

About ILLUMINATE-C Phase 3 Study

ILLUMINATE-C (NCT04152200 (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT04152200&esheet=52586745&newsitemid=20220301005123&lan=en-US&anchor=NCT04152200&index=3&md5=c5ca8f28e810b7da9dee85a911192080)) is a single arm, open-label, multinational Phase 3 study evaluating the safety and efficacy of lumasiran in PH1 patients of all ages with severe renal impairment (eGFR ≤ 45 mL/min/1.73m^2 or elevated serum creatinine for patients <12 months of age). The study is being conducted at 13 study sites across 10 countries around the world. Cohort A enrolled six patients with advanced PH1 who do not yet require dialysis, and Cohort B enrolled 15 patients who are hemodialysis-dependent. The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses. The primary efficacy endpoint for Cohort A was the percent change in plasma oxalate from baseline to month six, and the primary endpoint for Cohort B was the percent change in pre-dialysis plasma oxalate from baseline to month six. Key secondary endpoints are designed to evaluate additional measures of plasma oxalate and changes in urinary oxalate. Kidney function, frequency and mode of dialysis, frequency of kidney stone events, and measures of systemic oxalosis, including clinical manifestations, will also be evaluated in the extension period of the study.

About Primary Hyperoxaluria Type 1 (PH1)

PH1 is an ultra-rare genetic disease that affects an estimated one to three individuals per million in the United States and Europe. PH1 is characterized by oxalate overproduction in the liver. The excess oxalate 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 and nephrocalcinosis. 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.

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. By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function upstream of today’s medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing or disease pathway proteins, thus preventing them from being made. This is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases.

About Alnylam Pharmaceuticals

Alnylam (Nasdaq: ALNY) has led the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of people afflicted with rare and prevalent diseases with unmet need. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach yielding transformative medicines. Since its founding 20 years ago, Alnylam has led the *RNAi Revolution* and continues to deliver on a bold vision to turn scientific possibility into reality. Alnylam’s commercial RNAi therapeutic products are ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO® (lumasiran), and Leqvio® (inclisiran) being developed and commercialized by Alnylam’s partner Novartis. Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam is executing on its “*Alnylam P^{5}x25*” strategy to deliver transformative medicines in both rare and common diseases benefiting patients around the world through sustainable innovation and exceptional financial performance, resulting in a leading biotech profile. Alnylam is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com (https://cts.businesswire.com/ct/CT?

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Alnylam Forward Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, Alnylam's views with respect to the safety and efficacy of lumasiran as demonstrated by the six-month results of the ILLUMINATE-C Phase 3 study and the potential for lumasiran to substantially reduce plasma oxalate levels in patients with compromised renal function due to PH1, including those on hemodialysis, the potential for changes in plasma oxalate following treatment with lumasiran to positively impact long-term clinical outcomes, including those related to systemic oxalosis, the expected timing for FDA and CHMP review of regulatory filings for lumasiran, Alnylam's aspiration to become a leading biotech company and the planned achievement of its "Alnylam P^5x25" strategy, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam's efforts to mitigate the impact of the pandemic; the potential impact of the recent leadership transition on Alnylam's ability to attract and retain talent and to successfully execute on its "Alnylam P^5x25" strategy; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for its product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, including lumasiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling its approved products globally; delays, interruptions or

failures in the manufacture and supply of its product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication for OXLUMO or for ONPATTRO (and vutrisiran, if approved) in the future; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and the risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

This release discusses the use of a previously approved RNAi therapeutic in continued development and is not intended to convey conclusions about efficacy or safety as to these uses. There is no guarantee that the data described in this release will result in expanded use of this commercial product, or will gain health authority approval.

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