Alnylam Reports Positive Topline Results from ILLUMINATE-C Phase 3 Study of Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1

Jul 29, 2021

- Results Showed Substantial Reductions in Plasma Oxalate Relative to Baseline in PH1 Patients with Severe Renal Impairment, Including Those on Dialysis, and an Encouraging Safety and Tolerability Profile -

- Alnylam Intends to File Supplemental Regulatory Applications with the U.S. Food and Drug Administration and the European Medicines Agency Based on ILLUMINATE-C Results in Late 2021 -

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 29, 2021-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=45c3ace0c1a1f3537f64236b31cde47b) (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today positive topline results from the ILLUMINATE-C Phase 3 open-label study of lumasiran in patients of all ages with advanced primary hyperoxaluria type 1 (PH1) associated with progressive decline in renal function. Lumasiran is an RNAi therapeutic targeting hydroxyacid oxidase 1 (*HAO1*) – the gene encoding glycolate oxidase (GO) – that is being investigated for the treatment of adult and pediatric patients with advanced PH1. Results of the primary analysis at six months demonstrated substantial reduction in plasma oxalate from baseline in patients (N=21) with advanced disease, including those on hemodialysis. Elevated plasma oxalate is directly related to the pathophysiology of oxalosis and results in systemic deposition of oxalate in extra-renal tissues, potentially leading to bone fractures, cardiomyopathy, impaired erythropoiesis, vision loss, skin ulcers, and other serious manifestations[1]. The safety and tolerability profile of lumasiran following six months of treatment is encouraging across all ages, with no drug related serious adverse events (SAEs) and injection site reactions (ISRs) as the most common adverse event (AE).

“People with advanced PH1 suffer from severely impaired kidney function and may require an intensive dialysis regimen as a bridge to receiving a combined liver/kidney transplant – a procedure associated with high morbidity and lifelong immunosuppression. In ILLUMINATE-C, lumasiran reduced elevated levels of plasma oxalate that can lead to the morbidity and mortality associated with systemic oxalosis in this particularly vulnerable patient population,” said Jeroen Valkenburg, General Manager, Lumasiran program at Alnylam. “Through the ILLUMINATE clinical program, we are hoping to establish that lumasiran may be a therapeutic option for PH1 patients regardless of age or disease severity, including patients on hemodialysis. We look forward to reporting complete data from the ILLUMINATE-C study at a medical congress later this year.”

“Patients with PH1 face devastating health challenges, especially those approaching or experiencing kidney failure, and these new results from the ILLUMINATE clinical development program signal hope to some of the sickest and most severely impacted individuals in this patient community,” said Kim Hollander, Executive Director of the Oxalosis and Hyperoxaluria Foundation. “We’re thankful that Alnylam continues to drive forth research that may benefit the PH1 community and for conducting a study that has the potential to help those who have the most severe form of the disease.”

Results

ILLUMINATE-C (NCT04152200 (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT04152200&sheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=NCT04152200&index=2&md5=7046ccd5f6b85a4a0e22844eb59392f8)) 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), and 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. Renal function, frequency and mode of dialysis, frequency of renal stone events, and measures of systemic oxalosis, including clinical manifestations, will also be evaluated in the extension period of the study.

At six months, treatment with lumasiran resulted in a substantial reduction in plasma oxalate from baseline in both dialysis-independent and -dependent patients. Lumasiran also demonstrated positive results across key secondary endpoints, including measures of urinary oxalate (for patients in Cohort A) and additional measures of plasma oxalate. There were no deaths and no drug related SAEs among enrolled patients. There were two treatment discontinuations due to adverse events in the extension period of the study, neither of which was drug related. The most common drug related AEs (occurring in 10 percent or more of patients) were ISRs reported in five patients (23.8 percent), all of which were mild.

Based on these results, the Company plans to submit a Supplemental New Drug Application (sNDA) for lumasiran with the U.S. Food and Drug Administration (FDA) and a Type II Variation with the European Medicines Agency (EMA) in late 2021. In November 2020, lumasiran 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. Lumasiran is marketed in the U.S. and EU as OXLUMO®. ILLUMINATE-C topline results will be discussed during Alnylam's Second Quarter Earnings Conference Call on August 3rd at 8:30 am ET, and full results are expected to be presented at a medical meeting later this year.

About Lumasiran

Lumasiran is a subcutaneously administered RNAi therapeutic targeting hydroxyacid oxidase 1 (*HAO1*) in development for the treatment of 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®.

IMPORTANT SAFETY INFORMATION for OXLUMO (lumasiran)

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 Prescribing Information. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com%2Foxlumo-us-prescribing-information&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=Prescribing+Information.&index=3&md5=ac850ec6d1342375d48ee2db67cae74c)

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) is leading 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 genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS)/ocular 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 RNAi therapeutics platform. 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?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=www.alnylam.com&index=4&md5=4f7bfa541644885abaa0d0ffda534992) and engage with us on Twitter at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=%40Alnylam&index=5&md5=a4488340ae6907f65a77fa8634b6b682), on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2F48171%2F&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=LinkedIn&index=6&md5=167679f70b063688bd0c56e67d480050), or on Instagram (https://cts.businesswire.com/ct/CT?

id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=52467732&newsitemid=20210729005079&lan=en-US&anchor=Instagram&index=7&md5=18bdf4a35e2626692f327e61df3da904).

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 in the ILLUMINATE-C Phase 3 study and the potential for lumasiran to be a therapeutic option for PH1 regardless of age or disease severity, including for patients on hemodialysis, expectations regarding the timing of the presentation of full results from the ILLUMINATE-C Phase 3 study, and the timing and planned filing of supplemental applications with FDA and EMA based on the ILLUMINATE-C results, and 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; 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, 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 ONPATTRO 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 Quarterly Report on Form 10-Q 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, will successfully complete clinical development or will gain health authority approval.

Footnote:

[1] Milliner et al., End Points for Clinical Trials in Primary Hyperoxaluria. *Clin J Am Soc Nephrol*. 2020; 15(7):1056-1065.

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