November 3, 2017

Alnylam Reports Positive Preliminary Results from Ongoing Phase 1/2 Study of Lumasiran (ALN-GO1) in Patients with Primary Hyperoxaluria Type 1 (PH1)

- Lumasiran Achieves Substantial Reductions in Urinary Oxalate Levels in all Patients, Highlighting Potential of Substrate Reduction Therapy in PH1 through RNAi-mediated Glycolate Oxidase (GO) Inhibition -

- Lumasiran Generally Well Tolerated with No Treatment-Related Serious Adverse Events or Study Discontinuations up to Seven Months from Initial Dosing -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today positive preliminary data from its ongoing Phase 1/2 study with lumasiran (formerly known as ALN-GO1), an investigational RNAi therapeutic targeting glycolate oxidase (GO) for the treatment of Primary Hyperoxaluria Type 1 (PH1). Results were presented today at the American Society of Nephrology (ASN) Kidney Week 2017 Annual Meeting, being held October 31 to November 5, 2017 in New Orleans, Louisiana.

At ASN, Alnylam presented initial data from Part B of the Phase 1/2 study in the first two cohorts of patients with PH1 (6-19 years old) dosed with lumasiran or placebo (N=8). Part B is a randomized (3:1 drug:placebo), single-blind, placebo-controlled study in patients with PH1. Patients with relatively preserved renal function were enrolled to allow for measurement of urinary oxalate excretion as a marker for hepatic oxalate production. The reported data were as of the data cut-off date of October 3, 2017.

As compared to the one patient receiving placebo, preliminary results showed that the three patients in the first cohort - who received monthly subcutaneous doses of lumasiran at 1 mg/kg for three months - experienced greater than 50 percent decreases in urinary oxalate excretion relative to baseline. The placebo patient in the first cohort was subsequently given lumasiran at 1 mg/kg monthly for three months, and this patient experienced a similar reduction in urinary oxalate. The mean maximal reduction in urinary oxalate for all four patients in this initial low dose cohort was 66 percent, and all patients achieved urinary oxalate levels at or near the normal range. Moreover, lumasiran lowered urinary oxalate excretion below 1.1 mmol/24hrs/1.73m^2 - a threshold associated with reduced progression to end-stage renal disease in clinical studies* - in all patients with baseline excretion ≥ 1.6 mmol/24hrs/1.73m^2 (N=3). Patients in the second cohort are receiving monthly doses of lumasiran at 3 mg/kg or placebo for three months; this cohort is ongoing and remains blinded. Aggregate data (N=4) from Cohort 2 show a mean reduction of 47 percent in urinary oxalate output relative to baseline after the first of three doses. These initial results support the hypothesis that GO inhibition has the potential to reduce and possibly normalize levels of hepatic oxalate production, thus potentially halting PH1 disease progression.

"PH1 is a devastating disease, usually manifesting in early childhood, in which excessive hepatic oxalate production leads to renal failure and often death. In our initial study results with lumasiran in patients with PH1, we observed substantial reductions in urinary oxalate, a biomarker which is directly linked to disease pathology and has been correlated with both morbidity and disease progression. Accordingly, we believe these encouraging preliminary results validate our approach of targeting GO, a key liver enzyme in the pathway leading to excessive oxalate output in patients with PH1. Further, these results offer hope that investigational lumasiran may be a potential treatment option for patients afflicted by this life-threatening disease," said Pushkal Garg, M.D., Chief Medical Officer at Alnylam. "We now aim to discuss these data with regulators and advance lumasiran toward Phase 3 clinical studies, where we also plan to study patients with more severe manifestations of PH1, such as systemic oxalosis and renal failure. Indeed, we are working hard to expediently conduct the clinical studies necessary to gain a more thorough understanding of the full efficacy and safety profile of lumasiran in patients with PH1."

"Investigational lumasiran has the potential to be a paradigm-shifting approach in the treatment of patients with PH1, a severely debilitating and ultra-rare orphan disease that typically presents in early childhood," said Prof. Georges Deschênes, M.D., Ph.D., Hôpital Robert-Debré, an investigator in the ongoing lumasiran study. "The current standard of care for afflicted patients with advanced disease includes intensive dialysis and, ultimately, a combined liver/kidney transplant, as there are currently no approved medical interventions. Although only a small number of patients have been treated to date, the preliminary results from Part B of the study are very promising, showing evidence of oxalate reduction, and even normalization, with as few as three doses of lumasiran. With these promising initial data in patients who still have relatively healthy kidneys, the PH1 community is now interested in understanding the safety and efficacy of lumasiran in patients with more advanced disease, something that Alnylam plans to test."

Patients in the first cohort have been monitored for up to seven months after receiving their first dose of lumasiran with no drug-related serious adverse events (SAEs) or discontinuations from study. In all patients, lumasiran was generally well tolerated and the only drug-related adverse event (AE) reported was a mild and transient injection site reaction. Five SAEs were reported in three patients, including two episodes of renal stones and a case of pyelonephritis in a patient during placebo dosing. The two remaining SAEs were a report of renal stones and a case of dehydration associated with gastroenteritis, both of which occurred after dosing with lumasiran but were not considered drug-related.

*Zhao F. et al, Clin J Am Soc Nephrol. 2016; 11(1):119-26.

About Lumasiran Phase 1/2 Study
The Phase 1/2 trial of lumasiran is a randomized, single-blind, placebo-controlled study being conducted in two parts. Part A, now complete, was a single-dose study that enrolled 32 healthy adult volunteers in four single ascending dose cohorts (N=8 per cohort, randomized 3:1 drug:placebo), with subjects receiving lumasiran at dose ranges of 0.3 to 6 mg/kg. Data previously reported on Part A of the study showed that a single dose of lumasiran was generally well tolerated in healthy adult volunteers with dose-dependent elevations in plasma and urine glycolate, demonstrating preliminary human proof of concept. Part B is a multi-dose study designed to enroll up to 24 patients with PH1 (N=4 per cohort; 3:1 randomization of drug:placebo, with delayed lumasiran dosing for placebo). The primary objective of the study is to evaluate safety and tolerability of single and multiple subcutaneous doses of lumasiran. Secondary objectives include evaluation of pharmacokinetics and clinical activity of lumasiran as measured by its effects on plasma glycolate in normal healthy volunteers and urinary oxalate levels in patients with PH1.

About Lumasiran
Formerly known as ALN-GO1, lumasiran (pronounced "lu-MAH-si-ran") is an investigational RNAi therapeutic targeting glycolate oxidase (GO) in development for the treatment of Primary Hyperoxaluria Type 1 (PH1). Lumasiran is designed to reduce the hepatic levels of the GO enzyme, thereby depleting the substrate necessary for oxalate production, which 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 both U.S. and EU Orphan Drug Designations.

The safety and efficacy of lumasiran have not been evaluated by the U.S. Food and Drug Administration or any other health authority.

About Primary Hyperoxaluria Type 1 (PH1)
PH1 is an inborn error of metabolism. Specifically, PH1 is an autosomal recessive disorder of glyoxylate metabolism, where hepatic detoxification of glyoxylate is impaired due to mutation of the AGXT gene, which encodes the liver peroxisomal alanine-glyoxylate aminotransferase (AGT) enzyme, resulting in excessive oxalate production. Excess oxalate in PH1 patients results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of recurrent kidney stones or 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. Compromised kidney function exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and crystallization in bones, eyes, skin, and heart, leading to severe illness and death. About 50 percent of patients will have kidney failure by age 15, and about 80 percent will have end stage renal disease by age 30. Current treatment options for advanced disease are very limited, and include frequent renal dialysis or combined organ transplantation of liver and kidneys, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to Vitamin B6 supplementation, there are no approved pharmaceutical therapies for PH1.

Alnylam - Sanofi Genzyme Alliance
In January 2014, Alnylam and Sanofi Genzyme, the specialty care global business unit of Sanofi, formed an alliance to accelerate the advancement of RNAi therapeutics as a potential new class of innovative medicines for patients around the world with rare genetic diseases. The alliance enables Sanofi Genzyme to expand its rare disease pipeline with Alnylam's novel RNAi technology and provides access to Alnylam's R&D engine, while Alnylam benefits from Sanofi Genzyme's proven global capabilities to advance late-stage development and, upon commercialization, accelerate market access for these promising genetic medicine products. Sanofi Genzyme has the right to opt in to develop and commercialize lumasiran in territories outside of the United States, Canada and Western Europe and could elect to exercise its one right to a global license for lumasiran.

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 major new class of medicines, known as RNAi therapeutics, is on the horizon. 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 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, and hepatic infectious 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 and deep pipeline of investigational medicines, including four product candidates that are in late-stage development. 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 600 people in the U.S. and Europe and is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam or on LinkedIn.

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 potential for investigational RNAi therapeutics, including lumasiran, its expectations regarding the future development of lumasiran and its planned interactions with regulatory authorities to discuss the Phase 1/2 data and advance lumasiran into Phase 3 development, and expectations regarding its "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics, 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, Alnylam's ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its product candidates, the pre-clinical and clinical results for its product candidates, which may not be replicated or continue to occur in other subjects or in additional studies or otherwise support further development of product candidates for a specified indication or at all, actions or advice of regulatory agencies, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing, delays, interruptions or failures in the manufacture and supply of our product candidates, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its intellectual property rights against third parties and defend its patent portfolio against challenges from third parties, obtaining and maintaining regulatory approval, pricing and reimbursement for products, progress in establishing a commercial and ex-United States infrastructure, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage its growth and operating expenses, obtain additional funding to support its business activities, and establish and maintain strategic business alliances and new business initiatives, Alnylam's dependence on third parties for development, manufacture and distribution of products, the outcome of litigation, the risk of 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 other filings that Alnylam makes with the SEC. 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.

The scientific information discussed in this news release relating to Alnylam's investigational therapeutic, lumasiran, is preliminary and investigative. Lumasiran has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of lumasiran.

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