Alnylam Achieves Alignment with FDA on Accelerated Development Path for Lumasiran, an Investigational RNAi Therapeutic for the Treatment of Primary Hyperoxaluria Type 1 (PH1)

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− FDA Endorses Primary Endpoint of Reduction of Urinary Oxalate at Six Months for Pivotal Study Design −

− Company Intends to Initiate Lumasiran Phase 3 Study in Mid-2018, with Topline Results Expected in 2019 and, if Positive, an NDA Submission Anticipated in Early 2020 −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--May 3, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company has reached alignment with the U.S. Food and Drug Administration (FDA) on a pivotal study design for lumasiran, an investigational RNAi therapeutic for the treatment of primary hyperoxaluria type 1 (PH1). The Company and the FDA have aligned on a primary endpoint for the pivotal study based on reduction of urinary oxalate at six months, a biomarker directly linked to the pathophysiology of PH1 and known to be well correlated with disease progression. In addition, Alnylam and the FDA have aligned on a study size of approximately 25 patients with PH1. Based on the discussions with the FDA, the Company is on track to start the Phase 3 study in mid-2018 and is now guiding that it expects to report topline results in 2019 and, if positive, to submit an NDA in early 2020. Lumasiran was recently granted Breakthrough Therapy Designation from the FDA and Priority Medicines (PRIME) designation from the European Medicines Agency (EMA).

“Given the preliminary results reported to date, we believe that investigational lumasiran has the potential to prevent excessive oxalate production implicated in the pathophysiology and morbidity associated with PH1, an ultra-rare, life-threatening disease. We are very pleased with the FDA’s shared sense of urgency to evaluate the efficacy and safety of lumasiran as a potential therapeutic option for patients as rapidly as possible,” said Pritesh Gandhi, PharmD., Vice President and General Manager, Lumasiran program at Alnylam. “Indeed, we have now reached alignment with the FDA on a six-month primary endpoint based on reduction of urinary oxalate and a pivotal study sample size of approximately 25 patients. Based on this pivotal study design, and assuming positive results, we now expect to be in a position to submit an NDA in early 2020, which represents a significant acceleration in our efforts to bring this promising investigational medicine to patients.”

“Lumasiran offers hope to patients with PH1, who face devastating health challenges, as an investigational therapy with the potential to significantly reduce excessive oxalate production and prevent disease progression. Alnylam’s alignment on pivotal study design with the FDA is an important step forward for patients suffering from this severe disease, as it recognizes the urgency of the unmet need for an effective treatment for PH1 and lumasiran’s potential to fulfill this need,” said Kim Hollander, Executive Director, Oxalosis & Hyperoxaluria Foundation.

The ongoing Phase 1/2 Part B study is designed as a randomized, single-blind, placebo-controlled trial. Twenty patients with PH1, aged six and higher, were enrolled in Part B with enrollment now complete. In preliminary results presented at the American Society of Nephrology (ASN) Kidney Week 2017 Annual Meeting, lumasiran demonstrated a mean maximal reduction in urinary oxalate of 66 percent with monthly dosing at 1 mg/kg in the unblinded Cohort 1 of the study (N=4), with all patients achieving urinary oxalate levels at or near the normal range. Moreover, lumasiran lowered urinary oxalate excretion in all patients below a threshold well documented to be associated with reduced progression to end-stage renal disease. In addition, as of the ASN meeting data cutoff, aggregated and blinded data (N=4) from Cohort 2 showed a mean reduction of 47 percent in urinary oxalate excretion relative to baseline after the first of three monthly doses at 3 mg/kg. 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 serious AEs (SAEs) were reported in three patients, including two episodes of renal stones and a case of pyelonephritis in a patient receiving placebo. 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. None of the SAEs were considered drug-related.

About Lumasiran
Lumasiran (formerly known as ALN-GO1) 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, a Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA), and a Priority Medicines (PRIME) designation from the European Medicines Agency (EMA). The safety and efficacy of lumasiran have not been evaluated by the FDA, EMA or any other health authority.

About Primary Hyperoxaluria Type 1 (PH1)
PH1 is an ultra-orphan disease in which excessive oxalate production 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 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.

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 800 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.

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 potential for lumasiran to be a transformative treatment for patients with PH1, expectations regarding the pivotal study design and the expected timing to advance lumasiran into a pivotal study and to report topline results from that study, expectations regarding the timing of a potential NDA filing for lumasiran and regulatory review, Alnylam's plans for global commercialization of lumasiran, if approved, and expectations regarding "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 its 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 Annual Report on Form 10-K 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.

Lumasiran has not been approved by the FDA, EMA, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

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