Alnylam Expands Alnylam Act® Program to Improve Diagnosis of Primary Hyperoxaluria Type 1 (PH1) and Aligns with FDA on Trial Design for ILLUMINATE-B Phase 3 Pediatric Study of Lumasiran

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− Alnylam Act to Include No-Charge Third-Party Genetic Testing and Counseling for Adults and Children at Risk for PH1 –

− ILLUMINATE-B to Evaluate Safety and Efficacy of Lumasiran in PH1 Patients Under Six Years of Age –

− Company Reports on New Phase 1/2 Results That Demonstrate Sustained Reductions in Both Urinary and Plasma Oxalate –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 25, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that it has expanded the Alnylam Act® program to include no-charge, third-party genetic testing and counseling for adults and children who may have mutations in alanine-glyoxylate aminotransferase *(AGXT)*, the key gene known to be associated with primary hyperoxaluria type 1 (PH1), an ultra-rare, autosomal recessive disease characterized by pathologic overproduction of oxalate by the liver. Genetic testing available through Alnylam Act is provided by Invitae, an independent, third-party genetic testing company. The genetic test must be ordered by a healthcare professional and is available in the United States and Canada. Genetic counseling is provided by InformedDNA, an independent, third-party genetic counseling provider and is available in the U.S. only.

The Company also announced that it has aligned with the Food and Drug Administration (FDA) on a trial design for ILLUMINATE-B, a Phase 3 study of lumasiran, an investigational, subcutaneously administered RNAi therapeutic for the treatment of PH1. The study is an open-label study of lumasiran in eight PH1 patients under six years of age with relatively preserved renal function. The primary endpoint is percent reduction in urinary oxalate from baseline to six months, with long-term follow up of up to five years.

“PH1 is an inherited disease associated with progressive and irreversible decline in kidney function and severe systemic manifestations. We believe Alnylam Act can shorten the time to diagnosis and prevent misdiagnosis. Given the unpredictable and episodic course of this disease and its presentation at any age, genetic screening can accelerate diagnosis potentially allowing for early intervention, ahead of the need for organ transplantation – the only definitive current treatment option in patients with advanced disease,” said Pritesh J. Gandhi, PharmD., Vice President and General Manager, Lumasiran program at Alnylam. “We are also pleased to report that we have aligned with the FDA on the trial design for the ILLUMINATE-B study in pediatric patients, which will complement the recently initiated registrational trial, ILLUMINATE-A. These and other planned studies are aimed at assessing the safety and efficacy of lumasiran across the full spectrum of age and disease severity.”

“People with PH1 often experience delays in diagnosis, with the disease remaining unidentified for many years which can result in irreparable damage to the kidneys. The expansion of Alnylam Act will empower patients and their families by providing tools and resources to help them make informed decisions about their health and achieve earlier diagnosis,” said Kim Hollander, Executive Director, Oxalosis & Hyperoxaluria Foundation. “In addition, with most patients presenting in early childhood, we are pleased that Alnylam is aiming to conduct a study designed to address the pediatric PH1 population. We applaud Alnylam for their commitment to the PH1 community and their effort in improving care for adults and children impacted by this disease.”

In addition, Alnylam reported new results from the Phase 1/2 and Phase 2 open-label extension (OLE) studies of lumasiran at the American Society of Nephrology (ASN) 2018 Annual Meeting held on October 23-28 in San Diego, CA. Plasma oxalate data (N=10)* from the Phase 1/2 study were as of a data cut-off date of August 15, and demonstrated a 75 percent mean maximal reduction (range: 57-94 percent) relative to baseline. Fifty percent of patients achieved plasma oxalate levels within the normal range (less than 1.6 µmol/L). Reductions in plasma oxalate paralleled sustained reductions in urinary oxalate, which were previously reported at the 2018 European Society of Paediatric Nephrology (ESPN) Annual Meeting held October 3-6 in Antalya, Turkey; safety results for the Phase 1/2 study were also as reported at ESPN.

For those patients who have transitioned to the Phase 2 OLE study, which is designed to evaluate long-term safety and efficacy, the tolerability profile of lumasiran remains generally consistent with data from the Phase 1/2 study. Phase 2 OLE safety results (N=8) were based on a median study duration of 2.7 months (range: 0.03 to 3.02 months) since first dose. As of the data cut-off date of October 3, there were no discontinuations from study treatment. Serious adverse events (SAEs) were reported for two patients (25 percent), one with traumatic brain injury and contusion – sustained in a car accident – and one with nephrolithiasis**; none were assessed as related to study drug. Adverse events (AEs) were reported in five patients (63 percent); all were mild or moderate in severity and majority were assessed as unrelated to study drug. There were no reports of injection site reactions or clinically significant laboratory changes and increased glycolate levels were not associated with any safety findings.

*Number of patients with samples available for plasma oxalate assessment.
**SAE of nephrolithiasis occurred prior to patient receiving first dose of lumasiran in Phase 2 OLE study.

About Lumasiran Phase 1/2 Study Part B

The Phase 1/2 Part B study of lumasiran is a randomized (3:1 drug:placebo), single-blind, placebo-controlled evaluation of lumasiran in patients with PH1. In this multi-dose study, patients in Cohorts 1 and 2 received three monthly doses of lumasiran at 1 mg/kg or 3 mg/kg, respectively; Cohort 3 received two quarterly doses at 3 mg/kg. An additional eight patients received open-label lumasiran in expansions of each of the first two cohorts, totaling 20 patients enrolled. Patients randomized to the placebo group also received subsequent subcutaneous administration of lumasiran following administration of placebo. Patients had a mean age of 14.9 years (range: 6-43) and a mean estimated glomerular filtration rate (eGFR) of 77 mL/min /1.73m^2 (range: 42-131).

About the ILLUMINATE-A Phase 3 Study

The ILLUMINATE-A Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately 30 patients with a documented diagnosis of PH1. Patients will be randomized 2:1 to receive three monthly loading doses of lumasiran or placebo at 3 mg/kg followed by quarterly maintenance doses. The primary endpoint is the reduction of urinary oxalate at six months relative to baseline in the patients treated with lumasiran as compared to placebo. Key secondary and exploratory endpoints will evaluate additional measures of urinary oxalate, estimated glomerular filtration rate (eGFR), safety and tolerability, and quality of life. At month 6, the placebo patients will cross over to the lumasiran arm for long-term follow up out to 60 months. For more information on ILLUMINATE-A (NCT03681184) please visit clinicaltrials.gov, email clinicaltrials@alnylam.com or call 877-256-9526 in North America and +31 20 369 7861 in Europe.

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 hepatic levels of the GO enzyme, thereby depleting the substrate necessary for the 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 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 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. 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. Current treatment options are very limited and include frequent renal dialysis or combined organ transplantation of liver and kidney, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to Vitamin B6 therapy, 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 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 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) 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’s first U.S. FDA-approved RNAi therapeutic is ONPATTRO™ (patisiran) lipid complex injection available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. In the EU, ONPATTRO is approved for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a 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 worldwide 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 address the significant unmet need that PH1 represents, expectations regarding the expansion of Alnylam Act for adults and children at risk for PH1 and the possibility for increased diagnosis and disease awareness and earlier intervention, alignment with the FDA on the trial design for the ILLUMINATE-B Phase 3 pediatric study of lumasiran, 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, successfully launching, marketing and selling its approved products globally, Alnylam’s ability to successfully expand the indication for ONPATTRO in the future, 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.

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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