Alnylam Initiates ILLUMINATE-C Phase 3 Study of Lumasiran for the Treatment of Advanced Primary Hyperoxaluria Type 1 and Presents New Positive Results from Phase 2 Open-Label Extension Study

November 9, 2019

− Initial Results From ILLUMINATE-C Expected in Late 2020 –

− In Phase 2 OLE, Lumasiran Treatment Resulted in 76 percent Mean Maximal Reduction in Urinary Oxalate Relative to Phase 1/2 Baseline –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 9, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company has initiated ILLUMINATE-C, a new global Phase 3 study of lumasiran, an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of primary hyperoxaluria type 1 (PH1). The study will enroll patients of all ages with advanced renal disease, and the primary study endpoint is the percent reduction in plasma oxalate from baseline to six months. Alnylam expects to report initial ILLUMINATE-C results in late 2020.

The Company also announced new positive efficacy results from the ongoing Phase 2 open-label extension (OLE) study of lumasiran, which were presented at the American Society of Nephrology (ASN) 2019 Annual Meeting on Saturday, November 9 in Washington, DC.

"We are pleased to announce the start of the ILLUMINATE-C trial designed to assess the safety and efficacy of lumasiran in a PH1 patient population with advanced renal disease, including patients of all ages and those on dialysis. This study complements our comprehensive clinical development plan for lumasiran, led by our ILLUMINATE-A pivotal study with results expected later this year and our ILLUMINATE-B study in young pediatric patients. Given the heterogeneity of the PH1 population, the ILLUMINATE trials collectively address PH1 patients across the spectrum of age and disease onset and severity," said Pritesh J. Gandhi, PharmD, Vice President and General Manager, Lumasiran program at Alnylam. "We are also pleased to report new results from our Phase 2 OLE study, and are encouraged by the sustained reductions in urinary oxalate and by the overall safety profile of lumasiran observed to date."

The Phase 2 OLE results were reported as of the data cut-off date of September 12, 2019 and demonstrated a 76 percent mean maximal reduction (range: 43-91 percent) in urinary oxalate excretion relative to Phase 1/2 baseline values in all cohorts (N=19)*. In the study, all patients achieved a urinary oxalate level at or below 1.5 times the upper limit of normal (less than or equal to 0.69 mmoL/24hr/1.73m^2), and 68 percent of patients achieved a urinary oxalate level within the normal range (less than or equal to 0.46 mmol/24hr/1.73m^2). Patients also experienced an 82 percent mean maximal reduction in urinary oxalate:creatinine ratio (range: 62-94 percent) after lumasiran dosing across all cohorts (N=20).

The Phase 2 OLE safety results were based on a median study duration of 10.4 months (range: 7-17 months) since the first dose administered in the OLE study. As of the data cut-off date, there were no discontinuations from treatment. A single patient (1/20; 5 percent) reported two serious adverse events (SAEs) of traumatic brain injury and bone contusion sustained in a car accident; neither was assessed as related to study drug. There were no other reported SAEs in the OLE study. Adverse events (AEs) were reported in 19/20 (95 percent) patients; most were mild in severity and assessed as unrelated to study drug by the investigators. Injection site reactions, which were reported in 4/20 (20 percent) patients, were mild and did not affect dosing. Other AEs reported in more than one patient were: headache, oropharyngeal pain (N=3); gastroenteritis, viral gastroenteritis, pyrexia, and vomiting (N=2). There were no clinically significant laboratory changes.

To view the results presented by Alnylam at ASN 2019 Annual Meeting, please visit www.alnylam.com/capella.

*Patients who had a valid 24-hour urinary oxalate assessment.

About ILLUMINATE-C Phase 3 Study
The ILLUMINATE-C Phase 3 trial is a single-arm, open-label, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately 16 patients with a documented diagnosis of PH1. Cohort A will enroll patients with advanced disease who do not yet require dialysis and Cohort B will enroll patients who are dialysis-dependent. During the 6-month primary analysis period patients will receive three monthly doses of lumasiran followed by monthly or quarterly maintenance doses. The primary endpoint is the percentage change in plasma oxalate from baseline to six months. Key secondary endpoints will evaluate additional measures of plasma oxalate and changes in: urinary oxalate, renal function, nephrocalcinosis, frequency and mode of dialysis, frequency of renal stone events, and measures of systemic oxalosis. For more information on ILLUMINATE-C (NCT04152200) 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 is an investigational, 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 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-rare 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)/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 discovery platform. Alnylam’s first commercial RNAi therapeutic is ONPATTRO ® (patisiran), approved in the U.S., EU, Canada, Japan, and Switzerland. Alnylam has a deep pipeline of investigational medicines, including five 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 1,200 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 the potential for lumasiran to address the significant unmet needs of PH1 patients, its expectations regarding the timing for reporting results from the ILLUMINATE-A and ILLUMINATE-C clinical studies, its views regarding the ILLUMINATE trials collectively addressing PH1 patients across the spectrum of age and disease onset and severity, 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, including lumasiran, 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, including lumasiran, 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, including lumasiran, 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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