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

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− All Patients in Phase 1/2 Study Have Now Transitioned into Phase 2 OLE –

− Lumasiran Treatment Resulted in 72 Percent Mean Maximal Reduction in Urinary Oxalate Relative to Phase 1/2 Baseline –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 15, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today that the Company has initiated ILLUMINATE-B, a global Phase 3 pediatric study of lumasiran, an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of primary hyperoxaluria type 1 (PH1). The study will enroll approximately eight patients with PH1 under six years of age. The primary endpoint is the percent reduction in urinary oxalate from baseline to six months. The Company expects to report initial ILLUMINATE-B results in mid-2020.

The Company also announced new positive efficacy results from the ongoing Phase 2 open-label extension (OLE) study of lumasiran. The results were presented at the International Society of Nephrology (ISN) 2019 Annual Meeting held on April 13-16 in Melbourne, Australia.

“We are pleased to start the ILLUMINATE-B pediatric trial, an important step forward in our goal to assess the safety and efficacy of lumasiran across the PH1 age and disease severity continuum, including patients in early infancy. This study adds to our overall clinical development plan for lumasiran, led by our ILLUMINATE-A pivotal study with results expected by year-end 2019,” 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 consistently sustained reductions we observe in urinary oxalate and by the overall safety profile of lumasiran observed thus far.”

All patients (N=20) from the Phase 1/2 study of lumasiran have now transitioned to the Phase 2 OLE study designed to evaluate long-term safety and efficacy of lumasiran. The new Phase 2 OLE results were reported with 18 patients dosed in the OLE as of the data cut-off date of February 8. Patients were on a range of lumasiran doses and regimens (1.0 mg/kg monthly, 3.0 mg/kg monthly, and 3.0 mg/kg quarterly).

There were no discontinuations from study treatment. A single patient (1/18; 5.6 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. Adverse events (AEs) were reported in 12/18 (66.7 percent) patients. Injection site reactions were reported in 3/18 (16.7 percent) patients; all were mild and assessed as related to study drug. There were no clinically significant laboratory changes.

Lumasiran demonstrated a 72 percent mean maximal reduction (range: 41-90 percent) in urinary oxalate excretion relative to Phase 1/2 baseline values across all dose cohorts (N=9). The mean reduction relative to baseline at Day 85 was 69 percent (N=7). Lumasiran also demonstrated a mean maximal reduction in urinary 24-hour oxalate:creatinine ratio of 77 percent (range: 57-91 percent) relative to Phase 1/2 baseline values across all dose cohorts (N=10). The mean reduction relative to baseline at Day 85 was 70 percent (N=9).

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

About ILLUMINATE-B Phase 3 Study
The ILLUMINATE-B Phase 3 trial is an open-label, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately eight patients less than six years of age with a documented diagnosis of PH1. Dosing regimen will be based on patient weight. The primary endpoint is the reduction of urinary oxalate at six months relative to baseline. Key secondary and exploratory endpoints will evaluate additional measures of urinary oxalate, estimated glomerular filtration rate (eGFR), safety and tolerability, and quality of life. For more information on ILLUMINATE-B (NCT03905694) please visit www.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)/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 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 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 1,000 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 potency, durability and therapeutic index of lumasiran and 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-B clinical studies, 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 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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