# Alnylam Completes Enrollment for ILLUMINATE-A Phase 3 Study of Lumasiran in Patients with Primary Hyperoxaluria Type 1 (PH1)

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*− On Track to Report ILLUMINATE-A Topline Results in Late 2019 –*

*− In Addition, Company Reports Final Positive Results from Phase 1/2 Study of Lumasiran –*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 17, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today that it has achieved full patient enrollment in its ILLUMINATE-A Phase 3 study of lumasiran, an investigational RNAi therapeutic targeting glycolate oxidase for the treatment of adults and children with primary hyperoxaluria type 1 (PH1). The study enrolled patients across 16 sites in eight countries. Alnylam is on track to report topline results from ILLUMINATE-A expected in late 2019 and, if positive, to submit filings for global regulatory approvals starting in early 2020. The Company also announced complete positive results from its Phase 1/2 clinical study and reiterated positive results from its ongoing Phase 2 open-label extension (OLE) study of lumasiran. Results will be presented at the 2019 Oxalosis & Hyperoxaluria (OHF) International Workshop being held in Boston, on June 21-22.

“We are pleased to have reached two important milestones for our PH1 program, timely completion of enrollment in ILLUMINATE-A – our Phase 3 pivotal study in adults and children – and successful completion of our Phase 1/2 study with positive final results,” said Pritesh J. Gandhi, PharmD, Vice President and General Manager, Lumasiran program at Alnylam. “We look forward to reporting topline results from the ILLUMINATE-A study expected in late 2019 and believe that lumasiran has the potential to provide a clinically meaningful treatment option for patients living with PH1.”

“With positive Phase 1/2 results where oxalate reduction was observed for every patient and with ongoing ILLUMINATE Phase 3 trials, we are hopeful for the future of our PH1 patient community who have limited options available to them,” said Kim Hollander, Executive Director, Oxalosis & Hyperoxaluria Foundation. “We look forward to continuing to work with Alnylam as they advance lumasiran through multiple Phase 3 studies designed to address the full spectrum of patients affected by PH1.”

In final Phase 1/2 study results, lumasiran demonstrated a mean maximal reduction in urinary oxalate of 75 percent (range: 43-92 percent) relative to baseline across all cohorts (1 mg/kg monthly, 3 mg/kg monthly, and 3 mg/kg quarterly; N=20). At 28 days post the last dose, the mean reduction relative to baseline was 66 percent. All patients (100 percent) achieved oxalate lowering to less than 1.5 times upper limit of normal (less than or equal to 0.69 mmol/24hr/1.73m$^2$). Among patients receiving 3 mg/kg monthly or quarterly doses of lumasiran (N=12), 92 percent achieved urinary oxalate levels within the normal range (less than 0.46 mmol/24hr/1.73m$^2$). Furthermore, lumasiran-treated patients across all cohorts (N=20) experienced a mean maximal decrease of 77 percent (range: 50-95 percent) in the ratio of urinary oxalate to creatinine – an additional measure of oxalate reduction that addresses the variability that is inherent in 24-hour urine collections.

Lumasiran results showed an acceptable safety and tolerability profile, with PH1 patients on study for a median of 9.8 months (range: 5.6 to 15.2 months); there were no study discontinuations. Serious adverse events (SAEs) were reported for one patient (33 percent) receiving placebo and four patients (20 percent) receiving lumasiran; none were related to study drug. The placebo patient experienced acute pyelonephritis and kidney stones. The lumasiran patients with SAEs included one patient with vomiting, one patient with abdominal pain, fever and vomiting, one patient with gastroenteritis, and one patient with kidney stones. Adverse events (AEs) were reported in two (66.7 percent) patients during placebo dosing and 20 (100 percent) patients after lumasiran dosing. The majority of AEs were mild or moderate in severity and were assessed as unrelated to study drug. Severe AEs were reported in one (33 percent) patient during placebo dosing (acute pyelonephritis) and one (5 percent) patient after lumasiran dosing (kidney stone); none were considered related to study drug by investigator. AEs reported in more than three patients receiving lumasiran were pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); and rhinitis and nephrolithiasis (N=4 each). Self-limiting injection site reactions (ISRs) were reported in three (15 percent) patients receiving lumasiran; all mild or moderate and with none affecting dosing. Lumasiran was not associated with any clinically significant adverse laboratory findings, including liver function tests.

As previously reported, all patients (100 percent) who completed Phase 1/2 (N=20) continue dosing in the ongoing Phase 2 OLE phase of the study. As of February 2019, patients in the Phase 2 OLE study have received lumasiran for a median of four months (range: 0.03–8.36; N=18). Lumasiran dosing across all evaluable cohorts (N=9) resulted in mean maximal reduction in urinary oxalate of 72 percent (range: 41-90 percent) relative to Phase 1/2 baseline levels. Multiple doses of lumasiran demonstrated an acceptable safety and tolerability profile in patients with PH1, with no drug related SAEs and no discontinuations from study treatment.

The Company also recently presented a case study of a healthy human with mutations in the *HAO1* gene, a validated target for the treatment of PH1, as well as results from research on the diagnostic journey of PH1 at the 56$^{th}$ Congress of the European Renal Association (ERA) and European Dialysis and Transplant Association (EDTA) held on June 13-16, 2019 in Budapest, Hungary. To view the results presented by Alnylam at the ERA-EDTA Congress, please visit www.alnylam.com/capella.

**About the ILLUMINATE-A Phase 3 Study**
ILLUMINATE-A is a six month randomized, double-blind, placebo-controlled, global, multicenter Phase 3 study to evaluate the efficacy and safety of lumasiran in approximately 30 patients with a documented diagnosis of PH1, followed by a 54 month extension period where all patients will receive lumasiran. Patients are randomized 2:1 to receive three monthly doses of lumasiran or placebo at 3 mg/kg followed by quarterly maintenance doses. The primary endpoint is the percent change in 24-hour urinary oxalate excretion from months 3 to 6 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, plasma oxalate, estimated glomerular filtration rate (eGFR), safety and tolerability, and quality of life. At month 6, the patients receiving placebo will cross over to receive lumasiran for long-term follow up. 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 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/ocular diseases. Based on Nobel Prizewinning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. ONPATTRO® (patisiran) is the first-ever RNAi therapeutic approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults and by the EMA 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 in Phase 3 studies and one in registration. 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. Headquartered in Cambridge, MA, Alnylam employs over 1,200 people worldwide. 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 need that PH1 represents, its plans to present study data and plans and expected timing to report topline results from ILLUMINATE-A and, if positive, submit filings for regulatory approval, expectations regarding Alnylam’s 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, 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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