Alnylam Reports Positive Topline Results from ILLUMINATE-B Phase 3 Study of Lumasiran for the Treatment of Primary Hyperoxaluria Type 1 in Children Under the Age of Six

Sep 30, 2020

– First-Ever Study to Have Evaluated the Safety and Efficacy of an Investigational RNAi Therapeutic in Infants and Children Under the Age of Six –

– Lumasiran Demonstrated Clinically Significant Reduction in Urinary Oxalate Levels Relative to Baseline in Children as Young as Four Months Old –

– Safety and Tolerability Profile Consistent with That Observed in ILLUMINATE-A Phase 3 Pivotal Study –

– Full Results Planned to be Presented at the American Society of Nephrology Annual Meeting in October 2020 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 30, 2020-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=056f7f23e104805ed6a08b4c5cd2f7c9) (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today positive topline results from the ILLUMINATE-B pediatric Phase 3 study of lumasiran, an investigational RNAi therapeutic targeting *hydroxyacid oxidase 1 (HAO1)* – the gene encoding glycolate oxidase (GO) – in development for the treatment of primary hyperoxaluria type 1 (PH1). ILLUMINATE-B is now the seventh Phase 3 study of an RNAi therapeutic that has yielded positive results, and the first-ever study evaluating the safety and efficacy of this new class of medicines in children under the age of six, including infants.

“We are pleased to report these positive topline results that we believe hold promise for many families impacted by PH1. The safety and efficacy of lumasiran are consistent with that reported for the ILLUMINATE-A study in patients six and older, demonstrating that lumasiran can significantly reduce the hepatic production of oxalate across all ages, which we believe can thereby address the underlying pathophysiology of PH1,” said Pritesh J. Gandhi, PharmD., Vice President and General Manager, Lumasiran Program at Alnylam. “The current standard of care for young children and infants diagnosed with PH1 is burdensome, including the frequent need for gastrostomy tube placement to enable hyperhydration, and, for those who have progressed to advanced disease, the risks associated with performing dialysis and, ultimately, organ transplantation. Thus, we believe, a meaningful reduction in urinary oxalate levels has the potential to favorably impact disease progression and management in very young patients. We look forward to reporting complete data from the ILLUMINATE-B study at the ASN virtual congress later this fall.”

“The ILLUMINATE-B results signal hope for the many families with children whose lives are deeply impacted by PH1. This is especially encouraging given that children as young as a few months old could benefit from the therapeutic approach that lumasiran offers, curbing production of oxalate at its source,” said Kim Hollander, Executive Director of the Oxalosis and Hyperoxaluria Foundation. “We are grateful to Alnylam for their continued commitment to the PH1 community and for designing and successfully conducting a study that addresses a particularly vulnerable group of patients – young children and babies.”

ILLUMINATE-B Topline Study Results

ILLUMINATE-B (NCT03905694) (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT03905694&sheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=%28NCT03905694%29&index=2&md5=c99a9ac99f06c159c88c155882bc79a0) is a single arm, open-label, multicenter Phase 3 trial that enrolled 18 patients with PH1 under the age of six (range: 3-72 months), with an estimated glomerular filtration rate (eGFR) of greater than 45 mL/min/1.73 m^2 or normal serum creatinine if less than 12 months old, at nine study sites, in five countries around the world. Lumasiran was administered according to a weight-based dosing regimen. The primary efficacy endpoint of the study was the percent change from baseline to Month 6 in spot urinary oxalate:creatinine ratio averaged across Months 3 to 6. At six months, relative to baseline, lumasiran demonstrated a clinically meaningful reduction in spot urinary oxalate:creatinine ratio. Reduction of urinary oxalate relative to baseline was consistent across all three body weight categories (less than 10 kg; 10 kg to less than 20 kg, and 20 kg or higher). Lumasiran demonstrated positive results across secondary endpoints, including additional measures of urinary and plasma oxalate. There were no serious or severe adverse events related to study drug, and the overall safety and tolerability profile of lumasiran was consistent with that observed in the ILLUMINATE-A study. Full ILLUMINATE-B study results will be presented on October 22, 2020 at the ASN virtual congress.

Lumasiran has received U.S. and EU Orphan Drug Designations, Breakthrough Therapy and Rare Pediatric Disease Designations from the U.S. Food and Drug Administration (FDA), and a Priority Medicines (PRIME) designation from the European Medicines Agency (EMA). Alnylam has filed a New Drug Application (NDA) for lumasiran with the U.S. FDA. The FDA has granted a Priority Review for the NDA and has set an action date of December 3, 2020 under the Prescription Drug User Fee Act (PDUFA). In addition, the Marketing Authorisation Application (MAA) for lumasiran has been submitted to and validated by the EMA and has received Accelerated Assessment designation.

The Company is also conducting ILLUMINATE-C – a global single-arm Phase 3 study of lumasiran in PH1 patients of all ages with advanced renal disease, including patients on dialysis, with results expected in 2021.

About ILLUMINATE-A Phase 3 Study

ILLUMINATE-A (NCT03681184) (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT03681184&sheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=%28NCT03681184%29&index=3&md5=57a480024cc8e1eaabc00021e1d265ea) is a six-month randomized, double-blind, placebo-controlled, global, multicenter Phase 3 study (with a 54-month extension period) to evaluate the efficacy and safety of lumasiran in 39 patients with a documented diagnosis of PH1. Patients were randomized 2:1 to receive three monthly doses of lumasiran or placebo followed by quarterly maintenance doses at 3 mg/kg. The primary endpoint was the percent change in 24-hour urinary oxalate excretion from

baseline to the average of months 3 to 6 in the patients treated with lumasiran as compared to placebo. Treatment arms were stratified at randomization based upon mean 24-hour urinary oxalate during screening (≤ 1.7 or > 1.7 mmol/24hr/1.73m^2). Key secondary and exploratory endpoints were designed to evaluate additional measures of urinary oxalate, plasma oxalate, estimated glomerular filtration rate (eGFR), nephrocalcinosis, renal stone events, safety and tolerability.

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, Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA), and Priority Medicines (PRIME) designation from the European Medicines Agency (EMA). The safety and efficacy of lumasiran are under evaluation by the FDA and EMA.

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 or disease pathway 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 RNAi therapeutics platform. Alnylam's commercial RNAi therapeutic products are ONPATTRO® (patisiran), approved in the U.S., EU, Canada, Japan, Brazil, and Switzerland, and GIVLAARI® (givosiran), approved in the U.S, EU, and Brazil. Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam is executing 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 is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.alnylam.com%2F&esheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=www.alnylam.com&index=4&md5=3b888d74a19b566b09c09b9d9db23892) and engage with us on Twitter at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=%40Alnylam&index=5&md5=f5aa89662c356539caf4735f26a22bc3) or on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=52297167&newsitemid=20200930005038&lan=en-US&anchor=LinkedIn&index=6&md5=606b8f6fde49db441871c8250edf3754).

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 safety and efficacy of lumasiran as demonstrated in the ILLUMINATE-B Phase 3 study in children under the age of six, including infants, the potential for lumasiran to have a favorable impact on PH1 disease manifestations and overall disease progression and management across all ages, its plans to present the full results of the ILLUMINATE-B study, Alnylam's expectations with respect to the

review timelines for the lumasiran NDA and MAA by the FDA and EMA, respectively, Alnylam's plans, assuming favorable regulatory reviews, to bring lumasiran to patients with PH1 around the world, and expectations regarding the continued execution on its "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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by Alnylam products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to Alnylam's business, the effectiveness or timeliness of steps taken by Alnylam to mitigate the impact of the pandemic, and Alnylam's ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for its product candidates, including lumasiran, 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, or its marketed products; obtaining, maintaining and protecting intellectual property; intellectual property matters including potential patent litigation relating to its platform, products or product candidates; obtaining regulatory approval for its product candidates, including lumasiran, and maintaining regulatory approval and obtaining pricing and reimbursement for its products, including ONPATTRO and GIVLAARI; progress in continuing to establish a commercial and ex-United States infrastructure; successfully launching, marketing and selling its approved products globally, including ONPATTRO and GIVLAARI, and achieving net product revenues for ONPATTRO within its revised expected range during 2020; 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 within the ranges of guidance provided by Alnylam through the implementation of further discipline in operations to moderate spend and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to establish and maintain strategic business alliances and new business initiatives; Alnylam's dependence on third parties, including Regeneron, for development, manufacture and distribution of certain products, including eye and CNS products, Ironwood,

for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; 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.

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