Alnylam Reports Updated Positive Results from Phase 1/2 Study of Lumasiran in Patients with Primary Hyperoxaluria Type 1 (PH1)

June 8, 2018

− Patients Receiving Investigational Lumasiran Experienced Substantial and Sustained Reductions in Urinary Oxalate, Confirming Potential for RNAi-Mediated Inhibition of Glycolate Oxidase as a Robust Therapeutic Approach for PH1 –

− Lumasiran Generally Well Tolerated with no Treatment-Related Serious Adverse Events or Study Discontinuations –

− Company Remains on Track to Initiate Lumasiran Phase 3 Study in Mid-2018 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 8, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today new positive results from its Phase 1/2 study with lumasiran, an investigational RNAi therapeutic targeting glycolate oxidase (GO) for the treatment of Primary Hyperoxaluria Type 1 (PH1). Results were presented at the OxalEurope, European Hyperoxaluria Consortium, taking place on June 8, 2018 in Naples, Italy.

Updated interim data were from Part B of the Phase 1/2 study and were as of the data cut-off date of March 29, 2018. Part B is a randomized (3:1 drug:placebo), single-blind, placebo-controlled evaluation of lumasiran in patients with PH1. 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).

Lumasiran demonstrated a mean maximal reduction in urinary oxalate of 64 percent in patients enrolled in Cohorts 1-3 (N=12). All lumasiran-treated patients experienced a lowering in urinary oxalate below 0.7 mmol/24 hrs/1.73m^2, a threshold level associated with a reduced rate of progression to end-stage renal disease[1]. On day 85, patients receiving lumasiran (N=9) maintained a mean reduction in urinary oxalate of 63 percent (range: 49-73 percent). Alnylam believes the potent and durable reductions in urinary oxalate support a once quarterly, subcutaneous dose regimen. Further, these results continue to support the hypothesis that GO inhibition has the potential to reduce and possibly normalize levels of hepatic oxalate production, thus potentially halting PH1 disease progression. Dosing in Part B of the Phase 1/2 study is ongoing and eligible patients are transitioning into an open-label extension (OLE) study. The Company expects to present additional data from all cohorts as well as from the OLE study in late 2018.

“We are pleased to present data that signal hope to patients with PH1, an ultra-rare, life-threatening disease, with a profound unmet need. Given the encouraging results, we believe that lumasiran has the potential to alleviate the pathologic overproduction of oxalate, the metabolite that causes the severe, systemic manifestations of PH1. Furthermore, we believe these results validate our approach of targeting GO, a key liver enzyme involved in the excessive oxalate output in patients with PH1,” said Pritesh J. Gandhi, PharmD., Vice President and General Manager, Lumasiran program at Alnylam. “Based upon our recent discussions with the FDA, we are on track to advance this program into Phase 3 development at mid-year, with the goal of bringing lumasiran to patients around the world as rapidly as possible.”

“PH1 is an ultra-orphan disease, with a generally pediatric onset and an immediate need for an effective intervention. Today, patients with advanced disease have no choice but to undergo intensive dialysis and, ultimately, a dual liver/kidney transplant, with no other approved treatment alternatives in place,” said Prof. Bernd Hoppe, M.D., Head of the Division of Pediatric Nephrology, Department of Pediatrics, University of Bonn, Germany and an investigator in the lumasiran study. “The data presented on lumasiran provide evidence for oxalate reduction, highlighting the potential of this investigational medicine as an innovative approach for the treatment of patients with PH1.”

Lumasiran was generally well tolerated in all patients in the Phase 1/2 study (N=20). Fifteen (75 percent) of patients treated with lumasiran experienced an adverse event (AE); the majority of AEs were mild or moderate in severity and unrelated to study drug. AEs occurring in three or more patients included abdominal pain, headache, nasopharyngitis, pyrexia, and vomiting. Two patients reported injection site reactions, both of which were mild and transient. Two patients reported severe AEs; one patient had pyelonephritis during placebo dosing and one patient had a kidney stone with renal colic after lumasiran dosing. One patient receiving placebo and three patients receiving lumasiran reported serious adverse events (SAEs); none were assessed as related to study drug. The placebo patient experienced kidney stones and pyelonephritis. The lumasiran patients with SAEs included one patient with kidney stones, one patient with fever and abdominal pain, and one patient with gastroenteritis. Lumasiran has not been associated with any clinically significant adverse laboratory findings, and there were no study discontinuations due to AEs through the data cut-off date.

Alnylam recently announced alignment with the U.S. Food and Drug Administration (FDA) on a pivotal study design for lumasiran, including a primary endpoint at six months based on reduction of urinary oxalate, and a study size of approximately 25 patients with PH1. The Company has guided its intention to initiate the Phase 3 trial in mid-2018. Lumasiran has received Breakthrough Therapy Designation from the FDA and Priority Medicines (PRIME) designation from the European Medicines Agency (EMA).

1. Zhao F. *et al*., Clin J Am Soc Nephrol. 2016; 11(1):119-26.

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 the hepatic levels of the GO enzyme, thereby depleting the substrate necessary for oxalate production, which 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 FDA, and a Priority

Medicines (PRIME) designation from the 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 or 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. About 50 percent of patients will have kidney failure by age 15, and about 80 percent will have end stage renal disease by age 30. Current treatment options for advanced disease are very limited and include frequent renal dialysis or combined organ transplantation of liver and kidneys, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to Vitamin B6 supplementation, 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 major new class of medicines, known as RNAi therapeutics, is on the horizon. 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, and hepatic infectious 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 and 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 in the U.S. and Europe 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 be a transformative treatment for patients with PH1, expectations regarding the pivotal study design and the expected timing to advance lumasiran into a pivotal study and to report topline results from that study, expectations regarding the timing of a potential NDA filing for lumasiran and regulatory review, Alnylam’s plans for 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, 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20180608005154/en/

Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom, 617-682-4340
(Investors and Media)
or
Josh Brodsky, 617-551-8276
(Investors)