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Alnylam Reports Positive Interim Results from Ongoing Phase 1 Study of ALN-AS1, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

- In Asymptomatic High Excreter (ASHE) Porphyria Subjects, Single and Multiple Doses of ALN-AS1 Achieve Rapid, Dose-Dependent, and Durable Lowering of Toxic Heme Synthesis Intermediates, with Effects Sustained for Over Ten Months After a Single Dose -

- ALN-AS1 Generally Well Tolerated Following Single and Multiple Doses -

- ALN-AS1 Granted Orphan Drug Designation for the Treatment of Acute Hepatic Porphyrias by the United States Food and Drug Administration -

- Company to Discuss New Clinical Data during ALN-AS1 RNAi Roundtable on Tuesday, September 13 at 11:30 a.m. ET -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today interim data from its ongoing Phase 1 study with ALN-AS1, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias. These results were presented today during an oral presentation at the 2016 Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium, being held from September 6 - 9, 2016 in Rome, Italy. The new data were from Parts A and B of the ongoing Phase 1 study, which were conducted in asymptomatic "high excreter" (ASHE) subjects. ASHE subjects have a mutation in the porphobilinogen deaminase (PBGD) gene as found in acute intermittent porphyria (AIP) and have elevated levels of upstream toxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) that mediate porphyria attacks. Results demonstrated that single and once-monthly, subcutaneous administration of ALN-AS1 achieved rapid, dose-dependent, and durable lowering of ALA and PBG. Further, ALN-AS1 was found to be generally well tolerated. Alnylam is currently conducting Part C of the Phase 1 study in symptomatic AIP patients with recurrent porphyria attacks. Consistent with previous guidance, the Company plans to present initial porphyria biomarker data from Part C in late 2016, with potential clinical efficacy data on the frequency and severity of recurrent attacks expected in 2017.

"The acute hepatic porphyrias are a group of ultra-rare orphan diseases with enormous unmet medical need, where novel therapies are clearly warranted. Accordingly, we're very encouraged by these interim Phase 1 data in ASHE subjects, showing robust lowering of the toxic heme synthesis intermediates that mediate porphyria attacks," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of Research and Chief Medical Officer at Alnylam. "We also continue to be impressed by the durability of effect on these disease biomarkers following a single subcutaneous injection, which we believe to be supportive of a monthly or potentially once quarterly low volume dosing regimen. Importantly, ALN-AS1 has been generally well tolerated through the data transfer date. We very much look forward to the continued advancement of this novel compound, including initial data in symptomatic AIP patients with recurring porphyria attacks expected later this year."

New results include all available data as of the data transfer date of June 28, 2016. In Part A (N=20), subjects were enrolled in five single ascending dose (SAD) cohorts (N=4 per group, randomized 3:1, drug:placebo), receiving ALN-AS1 at doses from 0.035 to 2.5 mg/kg. In Part B (N=8), subjects were enrolled in two multiple ascending dose (MAD) cohorts (N=4 per group, randomized 3:1, drug:placebo), receiving two monthly subcutaneous doses of ALN-AS1 at 0.35 or 1.0 mg/kg. In both Parts A and B, ALN-AS1 administration resulted in rapid, dose-dependent, and durable silencing of liver ALAS1 mRNA. In addition, ALN-AS1 resulted in rapid and dose-dependent lowering of ALA and PBG of up to 95%. Reductions in ALA and PBG were highly durable, with effects lasting for over ten months after a single dose.

As of the data transfer date, ALN-AS1 continued to be generally well tolerated in ASHE subjects following single and multiple doses. There were three serious adverse events (SAEs) that were all deemed to be unlikely related to study drug. A total of 78 adverse events (AEs) were reported in both the SAD and MAD cohorts, of which 62 were determined to be not related or unlikely related to ALN-AS1 administration. With the exception of one AE, not related to study drug, that was severe, all other AEs were mild or moderate in severity, and most commonly included abdominal pain, diarrhea, hypoesthesia, nasopharyngitis, pruritis, and rash. Two mild and transient injection site reactions (ISRs) were reported. There were no clinically significant changes in vital signs, electrocardiograms, clinical laboratory parameters, or physical examination.

To view the ALN-AS1 clinical data described in this press release, please visit www.alnylam.com/capella.

Alnylam also announced today that the United States Food and Drug Administration (FDA) has granted Orphan Drug

Designation to ALN-AS1 for the treatment of acute hepatic porphyrias. The FDA Office of Orphan Products Development (OOPD) mission is to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions. The Orphan Drug Act provides incentives for sponsors to develop products for rare diseases. In July 2016, the European Medicines Agency (EMA) granted Orphan Drug Designation to ALN-AS1 for the treatment of acute hepatic porphyrias.

ALN-AS1 RNAi Roundtable Webinar Information
Alnylam will review these new clinical data and discuss acute hepatic porphyrias and plans for the further development of ALN-AS1 in an RNAi Roundtable webinar next Tuesday, September 13, 2016 at 11:30 a.m. ET. Speakers include:

- John Maraganore, Ph.D., Chief Executive Officer
- William Querbes, Ph.D., Associate Director, Research
- Guest Speaker: Herbert Bonkovsky, M.D., Professor of Gastroenterology at Wake Forest Baptist Medical Center and Scientific Advisory Board Member of the American Porphyria Foundation
- Guest Speaker: Ariel Lager, living with Acute Intermittent Porphyria

To register for the webinar, please visit www.alnylam.com/roundtables. A replay of the webinar and downloadable PDF of the presentation will be available on that website shortly after the Roundtable.

About the ALN-AS1 Phase 1 Study
The ALN-AS1 Phase 1 trial is being conducted in three parts. Parts A and B are randomized (3:1, drug:placebo), single-blind, single-dose (Part A) and multi-dose (Part B), dose-escalation studies, designed to enroll up to a total of 40 ASHE subjects. Per protocol, ASHE subjects in the study have a defined mutation in the PBGD gene and elevated urinary levels of ALA and PBG, but do not have a recent history of porphyria attacks or disease activity. The primary objective of Parts A and B is to evaluate safety and tolerability of single and multiple subcutaneous doses of ALN-AS1. Secondary objectives include evaluation of clinical activity for ALN-AS1 as measured by reduction in plasma and urinary levels of ALA and PBG. Exploratory objectives include the impact of ALN-AS1 on liver ALAS1 mRNA as measured from circulatory or excreted exosomal mRNA preparations in serum or urine, respectively. Part C is a randomized (3:1, drug:placebo), double-blind, multi-dose study in up to 12 AIP patients who experience recurrent porphyria attacks, to assess safety, tolerability, pharmacodynamics (i.e., lowering of serum and urine ALA and PBG, as well as liver ALAS1 mRNA) and clinical activity of multiple doses of ALN-AS1. In addition, this part of the study includes an exploratory evaluation of the effects of ALN-AS1 on the number and severity of attacks and other disease symptoms, use of hematin and pain medications, number and duration of hospitalizations, and quality of life.

About ALN-AS1
Alnylam is developing ALN-AS1, a subcutaneously administered, investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias, including acute intermittent porphyria (AIP). AIP is an ultra-rare autosomal dominant disease caused by loss of function mutations in porphobilinogen deaminase (PBGD), an enzyme in the heme biosynthesis pathway that can result in accumulation of toxic heme intermediates, including aminolevulinic acid (ALA) and porphobilinogen (PBG). Patients with AIP can suffer from acute and/or recurrent life-threatening attacks characterized by severe abdominal pain, neuropathy (affecting the central, peripheral or autonomic nervous system), and neuropsychiatric manifestations. ALN-AS1 is an ESC-GalNAc-siRNA conjugate targeting ALAS1, a liver-expressed, rate-limiting enzyme upstream of PBGD in the heme biosynthesis pathway. Inhibition of ALAS1 is known to reduce the accumulation of heme intermediates that cause the clinical manifestations of AIP. ALN-AS1 has the potential to be a prophylactic approach for the prevention of recurrent attacks, as well as for the treatment of acute porphyria attacks.

ALN-AS1 is an investigational compound, currently in early stage clinical development. The safety and efficacy of ALN-AS1 have not been evaluated by the U.S. Food and Drug Administration or any other health authority.

About Acute Hepatic Porphyrias
The porphyrias are a family of rare metabolic disorders with mostly autosomal dominant inheritance predominately caused by a genetic mutation in one of the eight enzymes responsible for heme biosynthesis. Acute hepatic porphyrias (AHP) constitute a subset where the enzyme deficiency occurs within the liver, and includes acute intermittent porphyria (AIP), hereditary coproporphyria, and variegate porphyria. Exposure of AHP patients to certain drugs, dieting, or hormonal changes can trigger strong induction of aminolevulinic acid synthase 1 (ALAS1), another enzyme in the heme biosynthesis pathway, which can lead to accumulation of neurotoxic heme intermediates that precipitate disease symptoms. Patients with AHP can suffer from a range of symptoms that, depending on the specific type, can include acute and/or recurrent life-threatening attacks with severe abdominal pain, peripheral and autonomic neuropathy, neuropsychiatric manifestations, cutaneous lesions and possibly paralysis and death if untreated or if there are delays in treatment. The only approved treatment for acute attacks is hematin (Panhematin® or Normosang®), a preparation of heme derived from human blood. Hematin requires administration through a large vein or a central intravenous line and is associated with a number of complications including thrombophlebitis or coagulation abnormalities. There are no approved therapeutics for prophylactic

use (i.e., the prevention of acute attacks), although hematin is sometimes used in this manner in patients who experience recurrent attacks. Chronic administration of hematin may result in renal insufficiency, iron overload, systemic infections (due to the requirement for central venous access) and, in some instances, tachyphylaxis.

Sanofi Genzyme Alliance
In January 2014, Alnylam and Sanofi Genzyme, the specialty care global business unit of Sanofi, formed an alliance to accelerate and expand the development and commercialization of RNAi therapeutics across the world. The alliance is structured as a multi-product geographic alliance in the field of rare diseases. Alnylam retains product rights in North America and Western Europe, while Sanofi Genzyme obtained the right to access certain programs in Alnylam's current and future Genetic Medicines pipeline, including ALN-AS1, in the rest of the world (ROW) through the end of 2019, together with certain broader co-development/co-commercialization rights and global product rights for certain products, including ALN-AS1.

About GalNAc Conjugates and Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugates
GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology enables subcutaneous dosing with increased potency and durability, and a wide therapeutic index. This delivery platform is being employed in nearly all of Alnylam's pipeline programs, including programs in clinical development.

About RNAi
RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of 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, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

About Alnylam Pharmaceuticals
Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines. Alnylam's pipeline of investigational RNAi therapeutics is focused in 3 Strategic Therapeutic Areas (STArs): Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics that address the major global health challenges of hepatic infectious diseases. In early 2015, Alnylam launched its "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, Alnylam expects to achieve a company profile with 3 marketed products, 10 RNAi therapeutic clinical programs - including 4 in late stages of development - across its 3 STArs. The company's demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Ionis, Novartis, Roche, Takeda, Merck, Monsanto, The Medicines Company, and Sanofi Genzyme. In addition, Alnylam holds an equity position in Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 200 peer-reviewed papers, including many in the world's top scientific journals such as *Nature, Nature Medicine, Nature Biotechnology, Cell, New England Journal of Medicine,* and *The Lancet*. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information about Alnylam's pipeline of investigational RNAi therapeutics, please visit www.alnylam.com.

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 RNAi investigational therapeutics, including ALN-AS1, its expectations regarding the timing of clinical studies and the expected timing for the presentation of clinical data from these studies, including from Part C of the ongoing Phase 1 study of ALN-AS1, its expectations regarding its STAr pipeline growth strategy, and its plans regarding 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 our 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.

The scientific information discussed in this news release relating to Alnylam's investigational therapeutic, ALN-AS1, is preliminary and investigative. ALN-AS1has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of ALN-AS1.

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