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Alnylam Receives European Medicines Agency PRIME Designation for Accelerated Assessment of Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today that the European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) scheme for givosiran (ALN-AS1), an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias. The purpose of the PRIME initiative is to bring treatments to patients faster by enhancing the EMA's support for the development of medicines for diseases where there is an unmet medical need and where early clinical data show potential to benefit patients.

Promising results from the Phase 1 study of givosiran formed the basis of the application for PRIME. The ongoing Phase 1 trial is being conducted as a randomized, double-blind, placebo-controlled study. Specifically, data were recently reported in patients with acute intermittent porphyria (AIP) experiencing recurrent attacks. As presented at the 2016 American Society of Hematology (ASH) meeting, givosiran demonstrated initial evidence for clinical activity in AIP patients with meaningful reductions in the number and frequency of porphyria attacks. In the first two dose cohorts, givosiran was found to be generally well tolerated with no drug-related serious adverse events. In the third dose cohort, which remains blinded, one death due to acute pancreatitis, considered unlikely related to givosiran or placebo, was reported after the data transfer date.

"We are pleased to have givosiran accepted into the PRIME program. We believe givosiran could be a potentially transformative treatment option for patients with acute hepatic porphyrias, a family of debilitating and life threatening diseases with enormous unmet medical need," said Jeff Miller, Vice President, General Manager, Givosiran Program at Alnylam. "We look forward to collaborating with the EMA on the accelerated assessment of givosiran, with the goal of advancing this investigational medicine into a Phase 3 trial in late 2017."

Givosiran has previously been granted Orphan Drug Designations in both the EU and the U.S. for the treatment of acute hepatic porphyrias. Through the PRIME program Alnylam will have enhanced scientific and regulatory support from the EMA, including its advice on optimization of the development pathway and the potential for accelerated assessment of the Marketing Authorisation Application (MAA).

About Givosiran
Alnylam is developing givosiran (formerly known as 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. Givosiran 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. Givosiran has the potential to be a novel treatment approach for the prevention of recurrent attacks. Givosiran is an investigational compound, currently in early stage clinical development. The safety and efficacy of givosiran 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 predominantly 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 (HCP), and variegate porphyria (VP). 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. There are no approved treatments for the prevention of attacks; the only approved treatment for acute attacks is hemin for

injection (Panhematin® or Normosang®), a preparation of heme derived from human blood. Hemin requires administration through a large vein or a central intravenous line and is associated with a number of complications including thrombophlebitis or coagulation abnormalities. Chronic administration of hemin may result in renal insufficiency, iron overload, systemic infections (due to the requirement for central venous access) and, in some instances, tachyphylaxis.

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 therapeutics, including givosiran, its expectations regarding the timing of clinical studies, including the initiation of a Phase 3 trial for givosiran following interactions with regulatory authorities, its expectations regarding scientific and regulatory support for givosiran from the EMA and collaborating with the EMA on the accelerated assessment of givosiran, its expectations regarding its STAr pipeline growth strategy, and 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, 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 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.

The scientific information referenced in this news release relating to givosiran is preliminary and investigative. Givosiran has 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 its safety or effectiveness.

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