Alnylam Initiates ENVISION Phase 3 Clinical Study with Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias (AHPs)

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? ENVISION will Include Interim Analysis with Reduction of Urinary Aminolevulinic Acid (ALA) as Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit ?

– Company Expects to Report Interim Analysis Results in Mid-2018 and to File NDA at or Around Year-End 2018, Representing Significant Program Acceleration –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 7, 2017-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today the initiation of the ENVISION Phase 3 clinical study with givosiran, a subcutaneously administered, investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias (AHPs). The Company is also reiterating its previous guidance that it expects to report interim analysis data in mid-2018 and, assuming positive results and pending U.S. Food and Drug Administration (FDA) review of the program at the time of the interim analysis, it intends to file a New Drug Application (NDA) for givosiran at or around year-end 2018.

Alnylam has also reached alignment on the ENVISION Phase 3 study design with the European Medicines Agency (EMA). Givosiran previously received Breakthrough Therapy designation by the FDA and PRIME designation by the EMA.

“The acute hepatic porphyrias are a family of ultra-rare, often misdiagnosed genetic diseases characterized by acute, potentially life-threatening attacks and debilitating multi-system symptoms; nearly 65% of patients suffer from chronic symptoms that result in a significantly diminished quality of life. The disease burden for these patients is dire and can include frequent hospitalizations, severe abdominal pain, neuropsychiatric symptoms, and weakness. The diagnosis of AHPs are often delayed an average of 15 years, further negatively impacting patients’ lives. A once-monthly, subcutaneous injection with acceptable tolerability and the potential to prevent porphyria attacks could be transformational for patients,” said Jeff Miller, General Manager of the givosiran program. “Based on our Phase 1 and Phase 2 open-label extension study results, we believe that givosiran could meaningfully reduce the frequency of attacks requiring hospitalizations and the need for hemin, with an encouraging tolerability profile. As a global, wholly owned program, we are committed to rapidly advancing givosiran and most importantly, if approved, delivering this novel therapy to AHPs patients in need of new options.”

ENVISION Phase 3 study design
The ENVISION Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study in more than 20 countries to evaluate the efficacy and safety of givosiran in approximately 75 patients with a documented diagnosis of AHPs. Patients will be randomized on a 1:1 basis to receive 2.5 mg/kg of givosiran or placebo subcutaneously administered monthly, over a 6-month treatment period. The primary endpoint is the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit or hemin administration at home over the 6-month treatment period. The planned interim analysis will evaluate reduction of a urinary biomarker – aminolevulinic acid (ALA) – in 30 patients after three months of dosing, as a surrogate endpoint reasonably likely to predict clinical benefit. Key secondary and exploratory endpoints will evaluate reductions in the hallmark symptoms of AHPs, such as pain, nausea, and fatigue, as well as impact on quality of life. All patients completing the 6-month treatment period will be eligible to continue on an open-label extension (OLE) study in which they will receive treatment with givosiran for up to 30 months.

About Givosiran
Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting ALAS1 for the treatment of AHPs, including acute intermittent porphyria (AIP). AIP is the most common of the hepatic porphyrias, an ultra-rare autosomal dominant disease caused by increased ALAS1 in the presence of downstream enzyme defects of the heme biosynthesis pathway resulting in accumulation of neurotoxic intermediates, 5-aminolavulinic acid (ALA) and porphobilinogen (PBG) that cause AHPs symptoms. Inhibition of ALAS1, a liver-expressed enzyme upstream of PBGD in the heme biosynthesis pathway, is known to reduce the accumulation of heme intermediates that cause the clinical manifestations of AIP. Givosiran has the potential to be the first novel treatment approach to effectively and consistently prevent attacks, reduce chronic symptoms, and decrease burden of disease. Givosiran has been granted Breakthrough Therapy designation by the FDA and PRIME designation by the EMA. These regulatory designations are intended to expedite the development and review of new drugs that treat serious or life-threatening diseases. Givosiran has also been granted orphan drug designations in both the U.S. and the EU for the treatment of AHPs. The safety and efficacy of givosiran have not been evaluated by the FDA, the EMA or any other health authority.

Givosiran utilizes Alnylam’s ESC-GalNAc-siRNA conjugate technology, which enables subcutaneous dosing with increased potency and durability. The clinical significance of this technology is under investigation.

About Acute Hepatic Porphyrias
Porphyrias are a family of rarely diagnosed diseases with mostly autosomal dominant inheritance primarily caused by a genetic mutation in one of the eight enzymes responsible for heme biosynthesis. AHPs constitute a subset where the enzyme deficiency occurs within the liver and includes AIP, hereditary coproporphyria (HCP), variegate porphyria (VP) and ALAD-deficiency porphyria (ADP). AIP is the most prevalent form of hepatic porphyrias with an estimated 5,000 patients in the U.S. and EU. Accumulation of ALAS1, an enzyme in the heme biosynthesis pathway, can lead to accumulation of neurotoxic heme intermediates that precipitate disease signs and symptoms ranging from a severe and potentially life-threatening event — most commonly characterized by severe abdominal pain, vomiting, constipation, tachycardia, neurological symptoms, and possibly paralysis and death if untreated or if there are delays in treatment — to chronic symptoms involving peripheral and autonomic neuropathy, neuropsychiatric manifestations, with frequent hospitalizations. A recently published natural history study, EXPLORE, demonstrated that nearly 2/3 of patients suffer from both acute attacks and chronic symptoms. The commonality of these symptoms across a wide range of diseases, as well as the low incidence of AHPs, can delay proper diagnosis and thereby add to the disease burden. Current treatment options do not prevent attacks, control chronic symptoms, or decrease the burden of disease; the only approved treatment for attacks is hemin, a preparation of heme derived from human blood. Hemin is used on demand for attacks and off-label as prophylactic therapy; it does not control chronic symptoms nor effectively and consistently prevent attacks and requires IV 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 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 600 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 the potential for givosiran for the treatment of patients with AHPs, expectations regarding the timing for initial clinical data from the interim analysis in the Phase 3 clinical study of givosiran and timing of a potential filing with the FDA for regulatory approval should such data be positive, and expectations regarding 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 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.

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 the safety or effectiveness of this investigational therapeutic.

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