Alnylam Completes Enrollment in ENVISION Phase 3 Study of Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias (AHPs)

August 21, 2018

− Enrollment Completed Ahead of Schedule, Eight Months After First Patient Randomized −

− Company Remains on Track to Report Interim Analysis Data by the End of September and Full Study Data in Early 2019 −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 21, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that it has achieved full patient accrual in its ENVISION Phase 3 study of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias (AHPs). Enrollment was completed with 94 AHP patients randomized across 36 sites in 18 countries, surpassing the initial target of approximately 75 patients due to high patient demand.

The Company reiterated its previous guidance that it expects to report topline results of the interim analysis by the end of September in support of a potential accelerated approval, and topline results on the primary endpoint of annualized attack rate after six months of treatment in early 2019. The interim analysis is based on lowering of urinary aminolevulinic acid (ALA) levels from approximately 30 patients at three months of treatment as a surrogate biomarker that is reasonably likely to predict clinical benefit. Pending Company and FDA review of the program at the time of interim analysis and assuming positive results and acceptable safety, the Company continues to expect to submit an NDA at or around year-end 2018, seeking an accelerated approval.

“We’re pleased to have completed enrollment in the ENVISION Phase 3 study, and we’re thankful to the porphyria community for their support in helping to raise awareness about the importance of clinical trials in rare diseases,” said Akin Akinc, Vice President and General Manager, Givosiran Program at Alnylam. “The fact that we achieved this important milestone significantly ahead of schedule – in addition to exceeding the initial enrollment target – highlights the urgent demand and high unmet need for novel therapies in this disease setting. We remain committed to advancing givosiran, which we believe has the potential to transform the treatment landscape for patients with AHPs.”

The ENVISION Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of AHPs. Patients were 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 – ALA – in approximately 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 are eligible to continue on an open-label extension (OLE) study in which they will receive treatment with givosiran for up to 30 months.

In April, Alnylam presented new results from the Phase 1 and Phase 1/2 open-label extension (OLE) studies of givosiran for the treatment of AHPs during the European Association for the Study of the Liver (EASL) Annual International Liver Congress in Paris, France.

About Acute Hepatic Porphyrias
Acute hepatic porphyrias (AHPs) are a family of rare, genetic diseases characterized by potentially life-threatening attacks and for many patients chronic debilitating symptoms that negatively impact daily functioning and quality of life. AHPs are comprised of four subtypes, each resulting from a genetic defect leading to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and ALAD-deficiency porphyria (ADP). These defects cause the accumulation of neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), with ALA believed to be the primary neurotoxic intermediate responsible for causing both attacks and ongoing symptoms between attacks. Common symptoms of AHPs include severe, diffuse abdominal pain, weakness, nausea, and fatigue. The symptoms of AHPs can often resemble that of other more common conditions such as irritable bowel syndrome, appendicitis, fibromyalgia, and endometriosis and consequently, patients afflicted with AHPs are often misdiagnosed or remain undiagnosed for up to 15 years. Currently, there are no treatments approved to prevent debilitating attacks and treat the chronic symptoms of the disease.

About Givosiran
Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyrias (AHPs). Monthly administration of givosiran has the potential to significantly lower induced liver ALAS1 levels in a sustained manner and thereby decrease neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG) to near normal levels. By reducing accumulation of these intermediates, givosiran has the potential to prevent or significantly reduce the occurrence of severe and life-threatening attacks, control chronic symptoms, and decrease the burden of the disease. Givosiran utilizes Alnylam’s Enhanced Stabilization Chemistry ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. Givosiran has been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) and PRIME designation by the European Medicines Agency (EMA). 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 are currently being investigated in the ENVISION Phase 3 clinical trial and ongoing Phase 1/2 OLE study and have not been evaluated by the FDA, the EMA or any other health authority.

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. RNAi therapeutics are a new class of medicines that harness the

natural biological process of RNAi. 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 in developing medicines to improve the care of patients with genetic and other diseases.

About Alnylam

Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to improve 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. ONPATTRO, available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults, is Alnylam's first U.S. FDA-approved RNAi therapeutic. Alnylam has a deep pipeline of investigational medicines, including three 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 worldwide 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 to meet unmet needs of AHP patients, a planned interim analysis and potential NDA filing for givosiran if such interim analysis is positive, ENVISION study completion, the timing of regulatory filings, 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, successfully launching, marketing and selling its approved products globally, 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, 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 evaluated 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.

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