Alnylam Completes Rolling Submission of New Drug Application to U.S. Food and Drug Administration (FDA) for Givosiran for the Treatment of Acute Hepatic Porphyria

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− First Potential Treatment Demonstrating Substantial Reduction in the Frequency of Porphyria Attacks –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 5, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today the completion of the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyria (AHP). Givosiran previously received Breakthrough Therapy Designation from the FDA and Orphan Drug Designation in the U.S. for AHP.

“We’re very pleased to have completed our NDA filing for givosiran, just 90 days since reporting our positive topline ENVISION Phase 3 study results, consistent with our commitment to bring givosiran to patients as rapidly as possible. ENVISION demonstrated that givosiran substantially reduced the annualized rate of composite porphyria attacks, relative to placebo, with an overall safety and tolerability profile that we believe is encouraging in the context of this high unmet need disease,” said Akin Akinc, Ph.D., Vice President and General Manager, Givosiran Program at Alnylam. “Based on these results, we believe givosiran has the potential to be a life-changing medicine for patients living with AHP. With this submission, we are now one step closer to achieving our goal of providing a new therapeutic option for the treatment of AHP. We look forward to working with the FDA and other global regulatory agencies to bring this medicine to patients.”

Givosiran has also been granted Priority Medicines (PRIME) Designation by the European Medicines Agency (EMA) and Orphan Drug Designation in the EU for AHP. Alnylam intends to file a Marketing Authorisation Application (MAA) in mid-2019.

About Givosiran

Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyria (AHP). 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), towards normal levels. By reducing accumulation of these intermediates, givosiran has the potential to prevent or 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. The safety and efficacy of givosiran were evaluated in the ENVISION Phase 3 trial with positive results; these results have not been evaluated by the FDA, the EMA or any other health authority.

About ENVISION Phase 3 Study

The ENVISION Phase 3 trial was a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of acute hepatic porphyria (AHP). The primary endpoint was reduction relative to placebo in the annualized rate of composite porphyria attacks, defined as those requiring hospitalization, urgent healthcare visit, or hemin administration at home, in patients with acute intermittent porphyria (AIP, the most common subtype of AHP) over six months. Key secondary and exploratory endpoints evaluated reductions in neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG), usage of hemin, symptoms of AHP, such as pain, nausea, and fatigue, as well as impact on quality of life. The trial enrolled 94 patients with AHP, at 36 study sites in 18 countries around the world and is the largest ever interventional study conducted in AHP. Patients were randomized 1:1 to givosiran or placebo, with givosiran administered subcutaneously at 2.5 mg/kg monthly. Upon completion of dosing in the double-blind period, all eligible patients (99 percent) enrolled in the ENVISION open-label extension (OLE) to receive givosiran on an ongoing basis.

About Acute Hepatic Porphyria

Acute hepatic porphyria (AHP) refers to a family of rare, genetic diseases characterized by potentially life-threatening attacks and for some patients chronic debilitating symptoms that negatively impact daily functioning and quality of life. AHP is 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 AHP include severe, diffuse abdominal pain, weakness, nausea, and fatigue. The nonspecific nature of AHP signs and symptoms can often lead to misdiagnoses of other more common conditions such as irritable bowel syndrome, appendicitis, fibromyalgia, and endometriosis, and consequently, patients afflicted by AHP often remain without a proper diagnosis for up to 15 years. In addition, long-term complications of AHP and its treatment can include chronic neuropathic pain, hypertension, chronic kidney disease and liver disease, including iron overload, fibrosis, cirrhosis and hepatocellular carcinoma. Currently, there are no treatments approved to prevent debilitating attacks or to treat the chronic manifestations of the disease.

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 new class of medicines, known as RNAi therapeutics, is now a reality. 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 new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system/ocular diseases. Based on Nobel Prizewinning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. ONPATTRO® (patisiran) is the first-ever RNAi therapeutic approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults and by the EMA for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including six product candidates in Phase 3 studies. 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. Headquartered in Cambridge, MA, Alnylam employs over 1,200 people worldwide. For more information, 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 treatment benefits of givosiran and potential for givosiran to impact the lives of patients, the safety and tolerability profile for givosiran, plans and expected timing for filing of an MAA, 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.

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