Alnylam Submits Marketing Authorization Application to the European Medicines Agency for Givosiran for the Treatment of Acute Hepatic Porphyria

July 1, 2019

− Patients Receiving Givosiran in Pivotal Phase 3 ENVISION Study had a 74 Percent Mean Reduction in Annualized Rate of Composite Porphyria Attacks Compared to Placebo –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 1, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, today announced the submission of a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyria (AHP).

Givosiran has been granted Priority Medicines (PRIME) Designation by the EMA as well as Orphan Designation in the European Union. Givosiran has also been granted an accelerated assessment by the EMA which is awarded to medicines deemed to be of major public health interest and therapeutic innovation, and the award is designed to bring new treatments to patients more quickly. Accelerated assessment potentially provides a reduced review timeline from 210 to 150 days once the MAA is filed and validated.

“Patients living with acute hepatic porphyria often suffer from chronic pain and unbearable, debilitating attacks, with limited treatment options available. Today’s announcement takes us a step closer to providing a new therapeutic option to patients in Europe,” said Akin Akinc, Ph.D., Vice President and General Manager, Givosiran Program at Alnylam. “We believe givosiran has the potential to be a transformative medicine for patients with acute hepatic porphyria and we look forward to working closely with the EMA to bring this innovative new medicine to patients and their families in Europe.”

Findings from the pivotal ENVISION Phase 3 study are included as part of the application and were presented in April 2019 at the 54th Annual International Liver Congress™ of the European Association for the Study of the Liver (EASL). In the ENVISION study, patients receiving givosiran had a 74 percent mean reduction in the annualized rate of composite porphyria attacks compared to placebo, with an acceptable overall safety and tolerability profile.

Givosiran has also previously received Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA) and Orphan Drug Designation in the U.S. for acute hepatic porphyria. A New Drug Application for givosiran has been submitted to the FDA.

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 five product candidates in Phase 3 studies and one in registration. 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.

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, 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20190701005257/en/

Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom
(Investors and Media)
+1-617-682-4340

Josh Brodsky
(Investors)
+1-617-551-8276

Fiona McMillan
(Media, Europe)
+44 1628 244960