Alnylam Announces Publication of Phase 1 Givosiran Data in The New England Journal of Medicine

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− Givosiran Associated with Substantial and Sustained Lowering of Neurotoxic Heme Synthesis Intermediates Implicated in Acute Intermittent Porphyria –

− Givosiran also Associated with Reduced Rate of Porphyria Attacks and Hemin Use –

− Topline Phase 3 Readout Expected in Early 2019, with a Rolling NDA Submission Initiated –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Feb. 6, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that results from the Phase 1 study of givosiran, an investigational, subcutaneous RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyria (AHP), were published online today in *The New England Journal of Medicine* (NEJM). The full manuscript, titled "Phase 1 Trial of an RNA Interference Therapy for Acute Intermittent Porphyria," will appear in the February 7, 2019 issue of NEJM.

In the Phase 1 study, the proportion of patients reporting adverse events (AEs) was similar across treatment groups with no clear relationship with givosiran dose. The majority of AEs were mild or moderate; the most common AEs included nasopharyngitis, abdominal pain, and diarrhea. Serious AEs (SAEs) were reported in six patients treated with givosiran (N=33), including – as previously reported – one fatal SAE of hemorrhagic pancreatitis, assessed as unlikely related to study drug by the study investigator. Additional unrelated SAEs included influenza infection, opioid bowel dysfunction, miscarriage, and two patients with abdominal pain. No SAEs were reported in the placebo group (N=10).

Results showed that basal ALAS1 messenger RNA (mRNA), aminolevulinic acid (ALA), and porphobilinogen (PBG) levels were associated with disease activity, with higher levels noted in those with recurrent attacks, confirming the central importance of liver ALAS1 induction and ALA and PBG in the pathophysiology of acute intermittent porphyria (AIP). Monthly givosiran administration resulted in sustained reductions of ALAS1 mRNA, urinary ALA, and PBG to near normal levels. In exploratory analyses, these reductions were associated with a 79 percent decrease in mean annualized attack rate and an 83 percent decrease in mean annualized hemin usage, compared with placebo.

"We are pleased to have our givosiran Phase 1 findings published in such a highly esteemed, peer-reviewed journal. Indeed, we are encouraged by the emerging safety and tolerability profile for givosiran, as well as the results of exploratory analyses suggesting favorable effects on porphyria attack rate and hemin use for acute attacks," said Akin Akinc, Ph.D., Vice President and General Manager, Givosiran Program at Alnylam. "With no treatment options currently approved for the prevention of porphyria attacks, we believe givosiran has the potential to make a meaningful difference in the lives of AHP patients."

"Acute intermittent porphyria is the most common subtype of AHP where patients experience recurrent, incapacitating, neurovisceral attacks requiring hospitalization or urgent medical attention. The Phase 1 results not only advance our understanding of the pathologic basis of AIP but they also signal hope to patients and their caregivers living with the tremendous burden of this disease and its current management," said Dr. Eliane Sardh, Karolinska Institutet, Karolinska University Hospital, Porphyria Centre Sweden, the lead author of the NEJM paper. "I look forward to continued evaluation of the safety and efficacy of givosiran in the ongoing OLE and Phase 3 studies."

Dosing of eligible patients is ongoing in the Phase 1/2 open-label extension (OLE) study. In addition, safety and efficacy of givosiran are being evaluated in the ongoing ENVISION Phase 3 trial, a randomized, double-blind, placebo-controlled pivotal study. The Company recently announced positive topline interim analysis results based on reduction of urinary ALA in 43 patients with AHP. Topline results from the complete 6-month double-blind portion of ENVISION, including annualized porphyria attack rate – the primary endpoint of the study – are expected in early 2019.

Rolling submission for a new drug application (NDA) has been recently initiated, with full clinical sections planned to be submitted in mid-2019, assuming positive results.

About Givosiran Phase 1 Study

The Phase 1 study of givosiran was conducted in three parts. Parts A and B were randomized, single-blind, single-dose (Part A) and multi-dose (Part B), dose-escalation studies that enrolled 23 subjects who were "chronic high excreters" (CHE). Per protocol, CHE subjects in the study had a defined mutation in the porphobilinogen deaminase (PBGD) gene and elevated urinary levels of ALA and PBG, but did not have a recent history of porphyria attacks or disease activity. Part C was conducted as a randomized, double-blind, placebo-controlled study in 17 patients with acute intermittent porphyria (AIP) who experienced recurrent porphyria attacks. Patients were initially followed in a 3-month run-in phase, where the number and frequency of porphyria attacks and levels of ALA and PBG were measured prospectively. Patients who experienced at least one porphyria attack during the run-in phase were then eligible to enter the 6-month treatment phase of the study, where they were randomized to receive 2 once-quarterly doses or 4 once-monthly doses of placebo or givosiran at doses of 2.5 or 5.0 mg/kg. During the treatment phase, the effects of placebo or givosiran on the number and frequency of porphyria attacks, as well as on the levels of ALA and PBG, were measured prospectively in a blinded manner and then compared to run-in phase results. Additional measures included safety, tolerability, hospitalizations, use of hemin, levels of ALAS1 mRNA, and givosiran pharmacokinetics. Hemin is an FDA-approved agent used to treat porphyria attacks when they occur. Following the treatment phase of the Phase 1 study, all patients were eligible to receive givosiran in an open-label extension study.

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 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), to near 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. 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 AHP. 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. 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 whole 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 (CNS)/ocular 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. Alnylam's first U.S. FDA-approved RNAi therapeutic is ONPATTRO® (patisiran) lipid complex injection available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. In the EU, ONPATTRO is approved 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 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 1,000 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 benefits of givosiran, plans to complete an NDA submission and pursue a full approval in 2019, assuming positive final results of the ENVISION Phase 3 study of givosiran, the expected timing of the report of topline full results from the ENVISION study, 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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