Alnylam Presents Updated Phase 1/2 Open-Label Extension (OLE) Results for Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyria

November 9, 2018

− Givosiran Demonstrated Sustained Clinical Activity, with an Over 90 Percent Decrease in Mean Annualized Porphyria Attack Rate, Relative to Baseline –

− Safety Profile Encouraging with up to 25 Months of Treatment –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 9, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company presented updated results from the ongoing Phase 1/2 open-label extension (OLE) study of givosiran, an investigational RNAi therapeutic, targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyria (AHP). The new data were presented at The Liver Meeting® 2018 of the American Association for the Study of Liver Diseases (AASLD) being held November 9-13 in San Francisco, CA.

“We are encouraged by the sustained clinical activity and safety profile of givosiran in the ongoing Phase 1/2 OLE study, now with up to over two years of dosing. We believe these results demonstrate clinically meaningful reductions in neurotoxic biomarkers, porphyria attack rate, and hemin usage, supporting the potential of givosiran to be an important treatment option for AHP patients,” said Akin Akinc, Vice President and General Manager, Givosiran Program at Alnylam. “We remain committed to bringing givosiran to patients as rapidly as possible, and are on course to initiate a rolling submission for an NDA by the end of 2018, and report topline results from the ENVISION Phase 3 pivotal study in early 2019.”

“Patients with acute hepatic porphyria not only endure potentially life-threatening neurovisceral attacks but often present with debilitating chronic symptoms and a severely diminished quality of life, highlighting the profound unmet need in this disease setting for both patients and their caregivers,” said Karl Anderson, M.D., FACP, University of Texas Medical Branch and an investigator in the ENVISION Phase 3 trial. “I am encouraged by the sustained clinical activity of givosiran and look forward to results of the ENVISION Phase 3 trial, evaluating the potential of this investigational RNAi therapeutic as a treatment option for AHP.”

Updated Phase 1/2 OLE Results
As of the data cut-off date of June 7, 2018, a robust treatment effect was maintained in givosiran-treated patients with continued dosing in the Phase 1/2 OLE study (N=16), with a mean time on treatment of 13.6 months and total time on treatment across the Phase 1 and OLE studies of up to 25 months. Monthly dosing at 2.5 mg/kg led to sustained lowering of aminolevulinic acid (ALA) and porphobilinogen (PBG) toward normal levels, with a mean reduction from baseline of 87 and 83 percent, respectively, at 12 months. In patients who received givosiran during the Phase 1 study and continued with givosiran dosing in the OLE study (N=12), mean reductions in annualized attack rate (AAR)* of 93 percent and annualized hemin use of 94 percent were observed, relative to pre-treatment results (measured in the Phase 1 blinded, prospective run-in period). Similarly, patients in the placebo arm of the Phase 1 study crossing over to givosiran treatment in the OLE study (N=4) experienced mean reductions in AAR of 95 percent and annualized hemin use of 98 percent. Seven of sixteen patients (44 percent) achieved an AAR of zero with a mean of 11.3 months on treatment; the average AAR during the run-in period for these seven patients was 15.2.

Serious adverse events (SAEs) were reported in four patients. Previously reported SAEs included: a patient with an upper extremity deep vein thrombosis, assessed as unlikely related to study drug by the investigator; and one patient who had an anaphylactic reaction after the third dose of givosiran, assessed as definitely related to study drug, which resolved with medical management. New SAEs included: a patient with two episodes of pyrexia related to a suspected Port-a-Cath infection and chlamydia bronchitis, assessed as unlikely related to study drug; and one patient with a change in mental status due to a possible glucocorticoid toxicity from an acute bacterial sinusitis, both of which were assessed as unlikely related to study drug. Adverse events (AEs) occurring in three or more patients included abdominal pain, fatigue, injection site erythema, nausea, myalgia, diarrhea, headache, and nasopharyngitis. Six patients had injection site reactions, all mild to moderate. No clinically significant increases in liver function tests or lipase levels were noted with continued dosing in the OLE study.

Results presented at AASLD can be viewed on the Capella section of the Alnylam website.

*Attacks requiring hospitalization, urgent health care visit or hemin administration, which is the attack rate definition used in the ENVISION Phase 3 trial.

About Givosiran Phase 1 Study
The Phase 1 study of givosiran (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, all patients were eligible to receive givosiran in an open-label extension study.

About the ENVISION Phase 3 Study
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 an AHP. Patients were randomized on a 1:1 basis to receive 2.5 mg/kg of givosiran or placebo subcutaneously administered monthly, over a six-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 six-month treatment period. Key secondary and exploratory endpoints will evaluate reductions in the hallmark symptoms of AHP, such as pain, nausea, and fatigue, as well as impact on quality of life.

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. 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 an AHP are often misdiagnosed or remain undiagnosed for an average of 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 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) 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 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 1000 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 initiate a rolling NDA submission in 2018 and pursue a full approval in 2019 based on the complete 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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Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
(Investors and Media)
Christine Regan Lindenboom, 617-682-4340
or
(Investors)
Josh Brodsky, 617-551-8276