Alnylam Presents Positive Complete Results from ENVISION Phase 3 Study of Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyria

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− Givosiran Achieved a 74 Percent Mean Reduction in Composite Annualized Attack Rate (AAR) Relative to Placebo, with Consistent Reductions Across all Components of Composite Endpoint and Subgroups –

− Treatment Effect Includes a 90 Percent Median Decrease in Composite AAR Relative to Placebo, with 50 Percent of Givosiran Patients Attack-Free –

− Ninety-Nine Percent of Patients Enrolled in Open-Label Extension Study –

− Alnylam to Host Conference Call Saturday, April 13th at 8:00 am ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 12, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today positive complete results from the ENVISION Phase 3 study of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyria (AHP). The clinical data are being presented in an oral presentation at the European Association for the Study of the Liver (EASL) International Liver Congress™ being heldApril 10-14 in Vienna, Austria.

The full ENVISION results demonstrated a 74 percent mean and 90 percent median reduction in the primary endpoint measure of annualized rate of composite attacks in patients on givosiran relative to placebo during the six-month double-blind period. In addition, givosiran achieved statistically significant positive results for five of nine secondary endpoints, with an overall safety and tolerability profile that the Company believes is encouraging, especially in this high unmet need disease. Adverse events (AEs) were reported in 89.6 percent of givosiran patients and 80.4 percent of placebo patients; serious adverse events (SAEs) were reported in 20.8 percent of givosiran patients and 8.7 percent of placebo patients. Ninety-three of 94 patients, or 99 percent, enrolled in the open-label extension (OLE) period of the study. Based on the ENVISION results, the Company plans to complete its rolling submission of a New Drug Application (NDA) and file a Marketing Authorisation Application (MAA) in mid-2019.

“Given the high unmet need in this disease setting, we are very pleased for the patients and families living with acute hepatic porphyria for whom these results signal hope for a potential new therapeutic option,” said Akshay Vaishnaw, M.D., Ph.D., President of R&D at Alnylam. “Givosiran substantially reduced the frequency of attacks, providing strong support for a treatment benefit, with a consistent effect across all components of the primary endpoint and all subgroups analyzed. In this disease with high burden and associated comorbidities, we’re encouraged by the overall tolerability profile. We firmly believe givosiran has the potential to be a transformative medicine for patients living with AHP.”

“Currently, there are no approved therapies aimed at preventing the painful, often incapacitating attacks and chronic symptoms associated with AHP,” said Manisha Balwani, M.D., M.S, Associate Professor of the Department of Genetics and Genomic Sciences and Department of Medicine at the Icahn School of Medicine at Mount Sinai and principal investigator of the ENVISION study. “The results from ENVISION are promising and demonstrate a strong treatment effect for givosiran, with reduction of attacks and improvement in patient-reported measures of overall health status and quality of life. Thus, givosiran represents a novel and targeted treatment approach that has the potential to make a significant impact on the lives of patients who are struggling with the disabling symptoms of this disease.”

Efficacy Results
Givosiran met the primary efficacy endpoint with a 74 percent mean reduction relative to placebo in the annualized rate of composite porphyria attacks, defined as those requiring hospitalization, urgent healthcare visit, or hemin administration, in patients with acute intermittent porphyria (AIP) over six months (p equal to 6.04×10^{-9}). There was a corresponding 90 percent median reduction in composite annualized attack rate (AAR), with a median AAR of 1.0 in givosiran patients compared with a median AAR of 10.7 in placebo patients. Fifty percent of givosiran-treated patients were attack-free during the six-month treatment period as compared to 16.3 percent of placebo-treated patients. The reductions in attack rates were observed across all components of the primary endpoint. The treatment benefit for givosiran compared to placebo was maintained across all pre-specified patient subgroups, including age, race, geography, historical attack rates, prior hemin prophylaxis status, disease severity, and other baseline characteristics.

Givosiran also demonstrated statistically significant differences in five of nine hierarchically tested secondary endpoints relative to placebo. These included mean reductions of:

- 91 percent in urinary aminolevulinic acid (ALA) in patients with AIP at three months (p equal to 8.74×10^{-14}).
- 83 percent in urinary ALA in patients with AIP at six months (p equal to 6.24×10^{-7}).
- 73 percent in urinary levels of porphobilinogen (PBG) in patients with AIP at six months (p equal to 8.80×10^{-7}).
- 77 percent in the number of annualized days on hemin in patients with AIP (p equal to 2.35×10^{-5}).
- 73 percent in composite AAR for patients with any AHP (p equal to 1.35×10^{-8}).

The remaining four secondary endpoints did not meet the prespecified criteria for statistical significance in hierarchical testing.

Safety and Tolerability
AEs were reported in 43/48 (89.6 percent) of givosiran patients and 37/46 (80.4 percent) of placebo patients.SAEs were reported in 10/48 (20.8 percent) of givosiran patients and 4/46 (8.7 percent) of placebo patients.SAEs in givosiran patients consisted of two cases of chronic kidney disease

(CKD; 4.2 percent), and one case (2.1 percent) each of asthma, device-related infection, gastroenteritis, hypoglycemia, abnormal liver function test, major depression, pain management, and pyrexia.Three SAEs in givosiran patients were reported as related to study drug: pyrexia, abnormal liver function test, and CKD (one case).The two SAEs of CKD noted above were considered serious due to elective hospitalization for diagnostic evaluation.There were no deaths in the study. One patient, described below, in the givosiran arm (2.1 percent) discontinued treatment due to an AE. AEs reported in greater than 10 percent of givosiran patients and seen more frequently compared to placebo were nausea (27.1 versus 10.9 percent), injection site reactions (16.7 versus 0 percent), CKD (10.4 versus 0 percent), and fatigue (10.4 versus 4.3 percent). Four of five of the patients with AEs reported as CKD had a prior history of CKD or a baseline estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2; no patients had clinically significant proteinuria and there were no treatment discontinuations due to renal AEs.

Liver transaminase increases greater than three times the upper limit of normal (ULN) or baseline were observed in 7/48 (14.6 percent) patients on givosiran and 1/46 (2.2 percent) patients on placebo; all had evidence of iron overload or liver disease at baseline. As previously reported and as noted above, one patient on givosiran discontinued treatment due to an increase in alanine aminotransferase (ALT) level greater than eight times ULN, a protocol-defined stopping rule; this elevation did not meet Hy's Law and subsequently resolved. In the other six givosiran-treated patients, peak ALT levels ranged from 3.0-5.4 times ULN and were not accompanied by bilirubin increases; the ALT elevations were asymptomatic and all events resolved with continued dosing (N=5) or after a brief pause in dosing (N=1).

Patient Perspectives
In exploratory measures of patient-reported outcomes, a greater proportion of patients reported an improvement in overall health status on givosiran (89 percent) than placebo (37 percent), as measured by the Patient Global Impression of Change (PGIC) Questionnaire. Similarly, patients on givosiran reported an overall higher level of treatment satisfaction on givosiran (72 percent) than placebo (14 percent) and an increased ability to perform activities of daily living, as measured by the Porphyria Patient Experience Questionnaire (PPEQ). Specifically, a greater proportion of patients on givosiran reported improvements in traveling for work or pleasure (35.1 versus 13.2 percent), participating in social activities (35.1 versus 7.9 percent), planning for future events (35.1 versus 10.5 percent), doing household chores (35.1 versus 5.3 percent), and exercising moderately (32.4 versus 5.3 percent), relative to patients on placebo.

To view the results presented by Alnylam at EASL, please visit https://www.alnylam.com/capella.

Conference Call Information
Alnylam management will discuss these results via a conference call on Saturday, April 13, 2019 at 8:00 am ET (2:00 pm CET). A slide presentation will also be available on the Investors page of the Company's website, www.alnylam.com, to accompany the conference call. To access the call, please dial 866-548-4713 (domestic) or 323-794-2093 (international) five minutes prior to the start time and refer to conference ID 3368636. A replay of the call will be available beginning at 11:00 am ET on the day of the call. To access the replay, please dial 888-203-1112 (domestic) or 719-457-0820 (international) and refer to conference ID 3368636.

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 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 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 treatment benefits of givosiran and potential for givosiran to impact the lives of patients, the safety profile for givosiran, plans and expected timing for completion of the rolling submission of an NDA and 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 Annual Report on Form 10-K 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.

Author Disclosures
Dr. Manisha Balwani (Principal Investigator in the ENVISION study) receives financial compensation as an advisory board member for Alnylam (the study sponsor and manufacturer of the study drug givosiran).

The Icahn School of Medicine at Mount Sinai ("ISMMS") holds issued and pending patents related to the study drug givosiran and has licensed these patents to Alnylam. As part of the license to Alnylam, ISMMS will receive payments from Alnylam, including a payment when givosiran entered Phase 3 clinical studies, as well as future payments if givosiran becomes a marketed treatment for acute hepatic porphyria. ISMMS, as well as the ISMMS faculty that are named inventors on the licensed patents, will benefit financially.

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