Alnylam Presents New Clinical Results for Givosiran at the 2019 International Congress on Porphyrins and Porphyrias

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− Porphyria Attack Reductions Observed in ENVISION Phase 3 Study Maintained with Ongoing Givosiran Dosing in Open-Label Extension (OLE) Study –

− In ENVISION Phase 3 Study, Patients Receiving Givosiran Reported Reduced Daily Worst Pain, a Cardinal Porphyria Symptom, and Givosiran Was Associated with Improvements in Patient-Reported Quality of Life Measures, Compared to Placebo –

− In Phase 1/2 OLE, Givosiran Treatment of up to 30 Months Demonstrated Sustained Clinical Activity with an Over 90 Percent Decrease in Mean Annualized Porphyria Attack Rate, Relative to Baseline –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 10, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company and its collaborators presented new clinical results at the 2019 International Congress on Porphyrins and Porphyrias (ICPP), held September 8-11, 2019 in Milan, Italy. Presentations included additional results from the ENVISION Phase 3 study and the Phase 1/2 open-label extension (OLE) study of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyria (AHP).

“The new results that we and our collaborators presented this week at ICPP reinforce our belief in the potential of givosiran to reduce the disease burden associated with AHP and to improve quality of life for patients,” said Akin Akinc, Ph.D., Vice President and General Manager, Givosiran Program at Alnylam. “Of note, patients in our open-label extension studies have continued to experience sustained reduction of both porphyria attacks and levels of toxic intermediates known to be causative of disease manifestations. Accordingly, we are hopeful that givosiran will continue to provide the potential for long term benefit for AHP patients.”

“AHP is a tremendously burdensome condition accompanied by disabling symptoms that have a profound impact on quality of life. To that end, the patient reported outcomes in response to givosiran treatment are highly encouraging, with patients reporting significantly less pain – a primary manifestation of this condition – less reliance on analgesic medication, improvements in their daily functioning, and ability to lead a more normal life,” said Laurent Gouya, M.D., Ph.D., Paris Diderot University, Head of Centre Français des Porphyries, investigator in ENVISION Phase 3 study. “With patients reporting a positive treatment experience and data suggesting an improved quality of life based on exploratory endpoints, I am hopeful for the AHP patient community and look forward to the continued evaluation of givosiran.”

ENVISION Phase 3 OLE Results
As of the data cut-off date of January 31, 2019, all eligible patients (N=93) from the ENVISION Phase 3 study of givosiran rolled over into the OLE phase of the study. Reduction in the composite porphyria attack rate with givosiran treatment, which had been observed in the ENVISION Phase 3 study as early as one month after dosing, was shown to be sustained with continued dosing in the OLE phase of the study. Sustained reduction in levels of aminolevulinic acid (ALA), an intermediate in the heme biosynthesis pathway believed to be the primary neurotoxic intermediate responsible for causing both porphyria attacks and ongoing symptoms in between attacks, was also observed with continued dosing. Rapid and sustained lowering of attack rate and ALA levels was also observed in placebo patients who crossed over after the six-month double blind phase of the ENVISION Phase 3 study to receive givosiran in the OLE phase of the study. Givosiran’s safety profile in the OLE phase has remained consistent with the profile observed in the double blind phase of the ENVISION study.

ENVISION Results of Select Patient Reported Outcomes
A number of patient reported outcomes were collected as secondary and exploratory measures in the ENVISION study. Daily worst pain did not achieve statistical significance based on the prespecified ANCOVA analysis (p equals 0.0530), however, the data were found to not be normally distributed. A post-hoc analysis of daily worst pain was therefore performed using the non-parametric stratified Wilcoxon test. Based on the non-parametric test, patients on givosiran had a significant reduction in daily worst pain (nominal p equals 0.0455). In exploratory analyses, the reductions in pain were accompanied by fewer days of use of both opioid and non-opioid analgesics. Givosiran did not impact daily worst fatigue or daily worst nausea at six months, although these assessments will be repeated at twelve months to explore the effects of longer term dosing.

Change from baseline at six months of the Physical Component Summary (PCS) of the Short Form 12 (SF-12) health and quality of life questionnaire was a secondary endpoint that showed a trend favoring givosiran compared to placebo (nominal p equals 0.0216). There was consistent evidence of effect favoring givosiran compared to placebo (nominal p less than 0.05 for each) in the SF-12 domains of bodily pain, social functioning, and role physical (a domain that assesses limitations in routine activity due to physical impairment). The Patient Global Impression of Change (PGIC) at six months was an exploratory endpoint. The majority (59 percent) of givosiran treated patients reported their health status as “very much improved” or “much improved” since the beginning of the study compared to 18 percent of placebo patients reporting their status as “much improved”. Similarly, the Porphyria Patient Experience Questionnaire (PPEQ) at six months was assessed as an exploratory endpoint. On all eight items of the PPEQ, a greater proportion of patients on givosiran, relative to patients on placebo, reported improvements. In particular, a higher proportion (67 percent versus 11 percent) of givosiran-treated patients versus those on placebo reported “always” or “most of the time” in response to the question about the role of the study drug in helping them return to a more normal life over the prior four weeks.

Updated Phase 1/2 OLE Results
As of the data cut-off date of April 19, 2019, 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 22.8 months and total time on treatment across the Phase 1 and OLE studies of up to 35 months. Substantial mean reductions in annualized attack rate (AAR) and in annualized hemin use of greater than 90 percent were observed, with evidence for sustained or potentially enhanced clinical activity with continued dosing. Five out of twelve patients (42 percent) who received givosiran during the Phase 1 study and continued with givosiran dosing in the OLE study and two out of four patients (50 percent) who had been in the placebo

arm of the Phase 1 study and crossed over to givosiran treatment in the OLE study achieved an AAR of zero for a mean of 18.1 and 24.9 months, respectively.

The overall safety profile of givosiran in the Phase 1/2 OLE as of the data cut-off date remains consistent with that previously reported. Serious adverse events (SAEs) were reported in six patients. Those SAEs not previously reported at earlier data cut-off dates included: one patient with synovitis, assessed as not related to study drug, and one patient with abdominal pain, assessed as unlikely related to study drug. No clinically significant laboratory changes, including liver function tests, were observed with ongoing dosing in the Phase 1/2 OLE study.

The Company and collaborators also presented additional results on a drug-drug interaction study with givosiran, recent analyses from the EXPLORE natural history study, data on patient journey to diagnosis, real-world analysis of illness burden and management, and an overview of AHP symptomology based on peer-reviewed publications and patient narratives.

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

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 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 Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. Alnylam's first commercial RNAi therapeutic is ONPATTRO® (patisiran), approved in the U.S., EU, Canada, and Japan. 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. 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 implications of the additional data from the ongoing Phase 3 and Phase 1/2 OLE studies of givosiran, including the potential treatment benefits of givosiran, the safety profile of givosiran, the potential for enhanced clinical activity with continued dosing, and the potential for givosiran to improve the quality of life of patients, Alnylam's 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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