Alnylam Presents New Positive Clinical Results for Givosiran, an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

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− In Randomized, Double-Blind, Placebo-Controlled Phase 1 Study, Monthly Givosiran Demonstrated an Over 80 Percent Lowering of Urinary Aminolevulinic Acid (ALA), a Disease Biomarker, and an Over 75 Percent Decrease in Mean Annualized Porphyria Attack Rate, Relative to Placebo −

− Evidence of Enhanced Clinical Activity with Long-Term Treatment of up to 22 Months in Ongoing Phase 1/2 Open-Label Extension (OLE) Study, with an Over 90 Percent Decrease in Mean Annualized Porphyria Attack Rate, Relative to Baseline Run-in Attack Rate −

− Clinical Activity and Safety Results Support Accelerated Efforts to Bring Givosiran to Patients with Acute Hepatic Porphyrias –

− Management to Discuss Results in Webcast Conference Call Today, Saturday, April 14 at 8:00 am ET −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 14, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced new results from the Phase 1 and Phase 1/2 open-label extension (OLE) studies of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias (AHPs). These results were presented at the European Association for the Study of the Liver (EASL) 53rd Annual International Liver Congress™, being held April 11-15, 2018 in Paris, France. New data from the ongoing EXPLORE natural history study were also presented.

“We view these new results with givosiran as very encouraging, since they demonstrate robust and what we believe to be clinically meaningful reductions in urinary ALA, porphyria attack rate, and hemin administration with continued dosing for up to nearly two years. We also believe our new data support use of a monthly dosing regimen for sustained reductions in ALAS1 mRNA and urinary ALA, with improved clinical activity. In sum, we believe the clinical activity and overall safety profile for givosiran continue to support an accelerated Phase 3 development plan,” said Akin Akinc, Vice President and General Manager, Givosiran Program at Alnylam. “In the meanwhile, we continue to enroll patients in the ENVISION Phase 3 pivotal study, which was initiated at the end of 2017. Further, we are pleased to announce today that we expect to enroll the thirtieth patient into ENVISION in the coming weeks in support of the planned interim analysis in mid-2018, which, if positive, would support a potential NDA filing for givosiran by end of this year.”

“People afflicted with acute hepatic porphyrias – a family of ultra-rare inherited disorders – suffer from potentially life-threatening neurovisceral attacks, accompanied by frequent need for urgent care and hospitalization, and often endure debilitating chronic symptoms. This is a disease with overwhelming burden and an arduous journey to diagnosis, with patients having a severely diminished quality of life,” said Karl Anderson, M.D., FACP, University of Texas Medical Branch. “There is no question that there is an urgent need for novel therapies that can offer new hope to these patients by preventing attacks, addressing the chronic manifestations of this condition, and reducing disease burden overall. I believe that the new results presented for givosiran are encouraging, and the medical community looks forward to the results of the pivotal Phase 3 study underway.”

Phase 1 Part C Study Results
Givosiran treatment led to rapid, dose-dependent, and durable lowering of induced ALAS1 mRNA in patients with recurrent attacks. Lowering of ALAS1 resulted in corresponding reductions in both aminolevulinic acid (ALA), believed to be the primary neurotoxic intermediate responsible for disease manifestations, and porphobilinogen (PBG). Compared with a once quarterly dose regimen, monthly dosing led to consistent and sustained lowering of ALA and PBG of greater than 80 percent, relative to baseline; increasing the monthly dose from 2.5 mg/kg to 5.0 mg/kg did not lead to further lowering of ALA and PBG levels. Monthly givosiran dosing at 2.5 mg/kg led to mean reductions in annualized attack rate (AAR)* of 83 percent and annualized hemin use of 88 percent, relative to placebo. Monthly dosing regimens led to enhanced clinical activity as compared to quarterly dosing. A continuous relationship between greater ALA lowering and AAR reduction was also observed.

Serious adverse events (SAEs) were reported in six patients receiving givosiran in the Phase 1 study; none were assessed as related to study drug. SAEs consisted of two patients with abdominal pain leading to hospitalization, and one patient each with miscarriage, opioid bowel dysfunction, and influenza infection. As previously reported, the remaining SAE occurred in a recurrent attack patient who died due to hemorrhagic pancreatitis complicated by a pulmonary embolism and following a recent hospitalization for bacteremia. There were no other discontinuations due to adverse events (AEs) and no clinically significant changes in clinical laboratory assessments.

Interim Phase 1/2 OLE Results
As of February 26, 2018, a robust treatment effect was maintained in givosiran-treated patients with extended dosing in the OLE study, with a total time on treatment across the Phase 1 and OLE studies of up to 22 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 AAR of 93 percent and annualized hemin use of 94 percent were observed, relative to the AAR and annualized hemin use recorded for these patients in the Phase 1 run-in period. The extent of these reductions in the OLE study exceeded that observed in response to givosiran treatment during the Phase 1 study, suggesting that extended dosing at 2.5 mg/kg monthly potentially leads to enhanced clinical activity. Patients in the placebo arm of the Phase 1 study crossing over to givosiran treatment in the OLE study (N=4) experienced mean reductions of greater than 90 percent in AAR and annualized hemin use, relative to the Phase 1 run-in and placebo treatment periods. For patients in the OLE study, seven of sixteen, or 44 percent, achieved an AAR of zero with a mean of 8.5 months on treatment; during the prospectively monitored run-in period, these same patients experienced a median AAR of 15.1 (range from 6.3 to 34.0).

SAEs were reported in two patients. One patient presented with upper extremity deep vein thrombosis, assessed as unlikely related to study drug due to the presence of an indwelling central venous catheter and a prior history of venous damage from chronic hemin use. One patient had an anaphylactic reaction after the third dose of givosiran (first dose in the OLE study), assessed as definitely related to study drug. The patient had a past history of asthma, oral allergy syndrome, and allergic reactions to acne cream and possibly latex gloves. The event resolved with medical management, and the patient discontinued from the study. AEs occurring in three or more patients included abdominal pain, nausea, injection site

erythema, headache, injection site pruritus, fatigue, and nasopharyngitis. No clinically significant increases in liver function tests or lipase levels were noted with ongoing dosing.

EXPLORE Natural History Study Results
Data as of November 21, 2017 from the EXPLORE natural history study were also presented at the conference. EXPLORE is the first observational, multinational, prospective study designed to characterize the natural history, clinical management and quality of life of AHP patients (N=112) with recurrent attacks (three or more attacks/year) or who receive hemin or gonadotropin-releasing hormone analogue prophylaxis to prevent attacks. Updated data from EXPLORE demonstrate that patients suffer from both acute attacks and chronic symptoms (in 65 percent of patients) in between attacks, that together result in a diminished quality of life. Patients in the EXPLORE study had an AAR of 3.7, inclusive of 46 percent of patients taking hemin prophylaxis, with a mean attack duration of 7.3 days. The majority of attacks (76 percent) were treated in a healthcare facility or with hemin.

All results presented at EASL can be viewed on the Capella section of the Alnylam website.

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

Conference Call
Alnylam management will discuss these results via conference call today, April 14, 2018 at 8:00 am ET. 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 6810175. A replay of the call will be available beginning at 11:00 am ET on April 14, 2018. To access the replay, please dial 888-203-1112 (domestic) or 719-457-0820 (international) and refer to conference ID 6810175.

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 Givosiran
Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyrias (AHPs). 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 significantly 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 AHPs. 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 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. The 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 AHPs are often misdiagnosed or remain undiagnosed for up to 15 years. Currently, there are no treatments approved to prevent debilitating attacks and treat the chronic symptoms 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 major new class of medicines, known as RNAi therapeutics, is on the horizon. 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, and hepatic infectious 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 and 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 800 people in the U.S. and Europe 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 data presented for givosiran, and the potential implications of such data for patients, its expectations regarding the timing of the enrollment of the thirtieth patient in the ENVISION Phase 3 study, a planned interim analysis and potential NDA filing for givosiran if such interim analysis is positive, 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, 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.

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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