June 26, 2017

Alnylam Reports New Positive Clinical Results for Givosiran (ALN-AS1), an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyrias

- In Randomized, Double-Blind, Placebo-Controlled Study, Givosiran Demonstrates Decreased Annualized Attack Rate and Hemin Usage -

- Initial Results from Ongoing Open Label Extension (OLE) Study Show Consistent Reductions in Porphyria Attacks with Continued Givosiran Treatment -

- Givosiran Administration Generally Well Tolerated with Treatment up to 12 Months -

- Company Plans to Initiate Phase 3 Clinical Program in Late 2017 -

- Management to Discuss New Clinical Data in Webcast Conference Call Today, Monday, June 26th at 8:00 a.m. ET -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today new positive interim results from Part C, cohorts 1-3, of its ongoing double-blind, randomized, placebo-controlled Phase 1 study, in addition to initial results from an open-label extension (OLE) study with givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias. These results were presented today in an oral presentation at the 2017 International Congress on Porphyrins and Porphyrias (ICPP), being held from June 25 - 28, 2017 in Bordeaux, France. Results provide evidence that givosiran has the potential to prevent porphyria attacks in patients with acute intermittent porphyria (AIP) suffering with recurrent attacks. Based on initial results from the OLE study, prolonged administration of givosiran appears to be associated with consistent reductions in the incidence of porphyria attacks. Givosiran administration was generally well tolerated with up to 12 months of treatment. In addition, the Company plans to present updated results from the EXPLORE natural history study of patients with acute hepatic porphyria who experience recurrent attacks.

"The acute hepatic porphyrias are a family of ultra-rare, under-diagnosed diseases caused by mutations in the heme synthesis pathway resulting in debilitating acute attacks and chronic manifestations including severe pain, and changes in mental status and weakness. There is significant unmet medical need for novel therapies that could prevent acute attacks and improve chronic disease manifestations," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D at Alnylam. "We believe these new interim results continue to demonstrate the potential for givosiran to achieve meaningful reductions in the frequency of porphyria attacks, as well as demonstrate tolerability with extended dosing. We look forward to further exploring givosiran's clinical activity and safety profile as we complete Part C of the Phase 1 study, which is now fully enrolled, and continue dosing in the OLE study."

"We believe that a long acting therapeutic agent that has the potential to prevent porphyria attacks and that can be administered via a once monthly, low volume, subcutaneous injection could be a potentially transformative treatment option for patients suffering with this debilitating and potentially life-threatening disease," said Jeff Miller, General Manager of the givosiran program. "Based on these encouraging interim results and with both Breakthrough Therapy and PRIME designations granted, we will continue to work with global regulatory authorities to rapidly advance givosiran toward regulatory filings and, if approved, to patients. To that end, we remain on track to initiate the givosiran Phase 3 program in late 2017."

New results presented at ICPP include all available data from cohorts 1-3 in Part C of the Phase 1 trial (N=12) and cohorts 1 and 2 (N=8) of the OLE study as of the data cutoff date of April 21, 2017. Givosiran achieved potent silencing of the ALAS1 mRNA, which resulted in robust and durable lowering of aminolevulinic acid (ALA) and porphobilinogen (PBG), the toxic heme intermediates that mediate acute attacks and chronic porphyria symptoms. In the first three unblinded treatment cohorts from Part C, givosiran-treated patients (N=9) experienced a mean 63 percent reduction in the annualized number of all porphyria attacks relative to the run-in period attack rate, with consistent effects observed across a wide range of baseline attack rates. Evaluating only attacks that were treated at a healthcare facility or with hemin, givosiran administration was associated with a mean 73 percent reduction in annualized attack rate relative to placebo during the treatment period. In addition, a 73 percent mean decrease in annualized hemin doses relative to the run-in period was reported. Finally, in a new analysis, the observed reduction in annualized attack rate was found to be associated with the degree of ALA and PBG lowering.

Initial results from cohorts 1 and 2 (N=8) of the givosiran OLE study were also presented; to date, all eligible patients have rolled over from the Phase 1 study to the OLE study. Longer-term treatment with givosiran was associated with consistent reductions in the annualized porphyria attack rate. In addition, preliminary evidence was obtained suggesting the potential for further reductions in the attack rate with extended dosing. Specifically, for the six OLE patients randomized to receive givosiran in Phase 1, the mean annualized attack rate during the Phase 1 treatment period was nine and this was reduced further to five in the OLE study with a mean follow up of 111 days. Further, in the two OLE patients randomized to receive placebo in Phase 1, no attacks have occurred as of the data cut-off date following givosiran administration in the OLE study, with a mean follow up of 31 days. The Company expects to continue enrollment and dosing of patients in the OLE study, and plans on reporting results at least once annually.

As of the data cutoff date, givosiran administration was generally well tolerated in recurrent attack AIP patients in cohorts 1-3 in Part C of the Phase 1 study and in cohorts 1 and 2 of the ongoing OLE study, with a mean of 169 and 111 days on study, respectively, and up to 12 months on givosiran. In Part C there were no drug-related serious adverse events (SAEs) or discontinuations due to adverse events (AEs). Excluding porphyria attacks, three patients had four SAEs; none were assessed as related to study drug. As previously reported, one death occurred in a patient in cohort 3 in the givosiran arm due to hemorrhagic pancreatitis complicated by a pulmonary embolism and following a recent hospitalization for bacteremia; the death was considered to be unlikely related to study drug by the investigator and the study's Safety Review Committee. During the Phase 1 treatment period, all randomized patients reported at least one AE. The majority of AEs were assessed as mild or moderate in severity. Twenty-five percent of patients had severe AEs, assessed as unrelated to study drug. AEs in three or more patients included: abdominal pain, headache, nasopharyngitis, nausea and vomiting. Four patients were assessed as having AEs possibly related to study drug, including injection site reaction (mild and self-limiting), hypersensitivity, myalgia, headache, moderate renal impairment (in a patient with a history of moderate renal impairment) and erythema. There were no other clinically significant changes in vital signs, electrocardiograms, clinical laboratory parameters (including liver function tests and lipase tests), or physical examination. The overall safety experience in the ongoing OLE study was consistent with results from the Phase 1 study. No SAEs (excluding porphyria attacks) or discontinuations due to AEs have been reported in the OLE study.

Data from the EXPLORE natural history study will also be presented at the conference. EXPLORE is a prospective, multinational, observational study characterizing the natural history and clinical management of AHP patients with recurrent attacks (3 or more attacks/year) or who receive hemin or gonadotropin-releasing hormone analogue prophylaxis to prevent attacks. A total of 112 patients with acute hepatic porphyria (AHP), of which 104 have AIP, were enrolled from 13 countries. Updated 12-month data from EXPLORE demonstrate that patients suffer from both acute attacks and chronic symptoms (64 percent of patients) in between attacks, that together result in a diminished quality of life. The annualized attack rate on study was approximately five attacks/person with a mean attack duration of seven days. The majority of attacks (77 percent) required treatment in the hospital, urgent healthcare facility or with hemin. An analysis of costs associated with AHP and recurrent attacks - the first analysis of its kind in AHP in the U.S. - revealed the average estimated annual expenditure per patient ranges from approximately $400,000 to $650,000. These analyses only incorporate direct costs, and do not reflect indirect costs, such as the cost associated with lost productivity for both patients and caregivers. Updated EXPLORE data will be presented on Wednesday, June 28th and the presentations will be posted to the Alnylam website in the Capella section.

Conference Call Details

Management will discuss these results via conference call on Monday, June 26, 2017 at 8:00 a.m. 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 877-312-7507 (domestic) or 631-813-4828 (international) five minutes prior to the start time and refer to conference ID 42943196. A replay of the call will be available beginning at 11:00 a.m. ET on June 26, 2017. To access the replay, please dial 855-859-2056 (domestic) or 404-537-3406 (international), and refer to conference ID 42943196.

About Givosiran Phase 1 Study

The ongoing portion of the Phase 1 study of givosiran (Part C) is being conducted as a randomized, double-blind, placebo-controlled study in up to 24 patients with AIP who experience recurrent porphyria attacks. Patients are initially followed in a 3-month run-in phase, where the number and frequency of porphyria attacks and levels of ALA and PBG are measured prospectively. Patients who experience at least one porphyria attack during the run-in phase are then eligible to enter the 6-month treatment phase of the study, where they are 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, are measured prospectively in a blinded manner and then compared to run-in phase results. Additional measures include 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 are eligible to receive givosiran in an open-label extension study.

About Givosiran

Alnylam is developing givosiran (formerly known as ALN-AS1), a subcutaneously administered, investigational RNAi therapeutic targeting ALAS1 for the treatment of AHP, including AIP. AIP is the most common of the porphyrias, an ultra-rare autosomal dominant disease caused by loss of function mutations in porphobilinogen deaminase (PBGD), an enzyme in the heme biosynthesis pathway that can result in accumulation of toxic heme intermediates, including ALA and PBG. Givosiran is an ESC-GalNAc-siRNA conjugate targeting ALAS1, a liver-expressed, rate-limiting enzyme upstream of PBGD in the heme biosynthesis pathway. Inhibition of ALAS1 is known to reduce the accumulation of heme intermediates that cause the clinical manifestations of AIP. Givosiran has the potential to be a novel treatment approach for the prevention of recurrent attacks. Givosiran has previously been granted PRIME designation which was established by the European Medicines Agency (EMA) to bring treatments to patients faster by enhancing the EMA's support for the development of medicines for diseases where there is an unmet medical need and where early clinical data show potential to benefit patients. Givosiran also received Breakthrough Designation by the U.S. Food and Drug Administration (FDA). Breakthrough Therapy designation is granted to expedite the development and review of new drugs that treat serious or life-threatening diseases where preliminary clinical evidence exists in support of substantial benefit over available therapies. The designation is aimed to help ensure that patients with unmet medical needs receive access to new therapies through FDA approval as soon as possible. In addition, Givosiran has been granted Orphan Drug Designations in both the E.U. and the U.S. for the treatment of acute hepatic porphyrias.

The safety and efficacy of givosiran have not been evaluated by the FDA, the EMA or any other health authority.

About Acute Hepatic Porphyrias

The porphyrias are a family of rare metabolic disorders with mostly autosomal dominant inheritance predominantly caused by a genetic mutation in one of the eight enzymes responsible for heme biosynthesis. Acute hepatic porphyrias (AHP) constitute a subset where the enzyme deficiency occurs within the liver, and includes acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP) and ALAD-deficiency porphyria (ADP). Exposure of AHP patients to certain drugs, dieting, or hormonal changes can trigger strong induction of aminolevulinic acid synthase 1 (ALAS1), another enzyme in the heme biosynthesis pathway, which can lead to accumulation of neurotoxic heme intermediates that precipitate disease symptoms. Patients with AHP can suffer from a range of symptoms that, depending on the specific type, can include acute and/or recurrent life-threatening attacks with severe abdominal pain, peripheral and autonomic neuropathy, neuropsychiatric manifestations, cutaneous lesions and possibly paralysis and death if untreated or if there are delays in treatment. There are no approved treatments for the prevention of attacks; the only approved treatment for acute attacks is hemin for injection (Panhematin® or Normosang®), a preparation of heme derived from human blood. Hemin requires administration through a large vein or a central intravenous line and is associated with a number of complications including thrombophlebitis or coagulation abnormalities. Chronic administration of hemin may result in renal insufficiency, iron overload, systemic infections (due to the requirement for central venous access) and, in some instances, tachyphylaxis.

About RNAi

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of 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, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

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 patients who have limited or inadequate treatment options. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of 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 three product candidates that are in late-stage development or will be in 2017. 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. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam.

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 for RNAi therapeutics, including givosiran, its expectations regarding the timing of clinical studies, including the initiation of a Phase 3 trial for givosiran following interactions with regulatory authorities, its expectations regarding scientific and regulatory support for givosiran from the FDA and EMA and collaborating with these agencies on the accelerated assessment of givosiran, its expectations regarding the potential impact givosiran may have on reducing the economic burden of AHP for patients and their caregivers, its 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 our 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 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.

The scientific information referenced in this news release relating to givosiran is preliminary and investigative. Givosiran has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding its safety or effectiveness.

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