December 3, 2016

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

- In First Cohort (N=4) of Porphyria Patients with Recurrent Attacks, Givosiran Achieves a 74% Mean Decrease in Annualized Attack Rate -

- Company to Meet with Regulatory Authorities for Potential Phase 3 Start in Late 2017 -

- Management to Discuss New Clinical Data in Webcast Conference Call Tomorrow, Sunday, December 4 at 1:00 p.m. ET -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced positive initial results from Cohorts 1 and 2 of Part C of its Phase 1 study with givosiran (gi-VOH-si-ran), the International Nonproprietary Name for ALN-AS1, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias. These results were presented today in a poster at the 58th Annual Meeting of the American Society of Hematology (ASH), held December 3 - 6, 2016 in San Diego, California.

Part C of the Phase 1 study is a randomized, double-blind, placebo-controlled study in patients with acute intermittent porphyria (AIP) experiencing recurrent attacks. Results demonstrated robust and durable lowering of aminolevulinic acid (ALA) and porphobilinogen (PBG), the toxic heme intermediates that are believed to mediate porphyria symptoms and acute attacks. Moreover, in the first unblinded treatment cohort, givosiran demonstrated initial evidence for clinical activity in AIP patients with meaningful reductions in the number and frequency of porphyria attacks. In addition, aggregated and currently blinded results from the second cohort provided further evidence for clinical activity. In the first two dose cohorts, givosiran was found to be generally well tolerated with no drug-related serious adverse events. In the third dose cohort, which remains blinded, one death was reported after the data transfer date due to acute pancreatitis complicated by a pulmonary embolism and following an earlier hospitalization for bacteremia; the death was considered to be unlikely related to givosiran or placebo by the investigator and the study's Safety Review Committee. The Company plans to initiate a Phase 3 study in late 2017, subject to successful global regulatory interactions.

"Acute hepatic porphyrias are a group of ultra-rare orphan diseases with enormous unmet medical need. There are currently no approved or optimal treatment options for the prevention of recurrent attacks, and novel therapies are greatly needed. We believe these initial results from the first unblinded cohort of patients with AIP show that givosiran has the potential to achieve meaningful reductions in the number and frequency of porphyria attacks. These initial results were supported further with aggregated data from the second cohort of AIP patients, who currently remain blinded to treatment allocation. We look forward to further exploring givosiran's clinical activity, safety, and tolerability in two additional dose cohorts, which are now fully enrolled," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D and Chief Medical Officer of Alnylam. "We believe that a therapeutic agent that can prevent attacks and that could be administered via a low volume, subcutaneous injection once-monthly or quarterly has the potential to be a transformative treatment option for patients with this debilitating and potentially life-threatening disease. Based on these encouraging early results, we plan to meet with regulatory authorities with the goal of advancing this investigational medicine into a Phase 3 trial in late 2017."

Study Design
The Phase 1 study of givosiran is being conducted in three parts. Parts A and B, which have completed dosing, were randomized, single-blind, single-dose (Part A) and multi-dose (Part B), dose-escalation studies that enrolled 23 subjects who were "asymptomatic high excreters" (ASHE). Per protocol, ASHE subjects in the study have a defined mutation in the porphobilinogen deaminase (PBGD) gene and elevated urinary levels of ALA and PBG, but do not have a recent history of porphyria attacks or disease activity. Interim data from Parts A and B were presented at the Society for the Study of Inborn Errors of Metabolism (SSIEM) meeting in September 2016. Part C is a randomized (3:1, drug:placebo), double-blind, multi-dose study in up to 20 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.

Clinical Activity Results

Initial results from Part C presented at ASH include all available data as of the data transfer date of November 7, 2016. Data presented include unblinded results for Cohort 1 (N=4, 2.5 mg/kg given once-quarterly) and aggregated, blinded results for Cohort 2 (N=4, 2.5 mg/kg given once-monthly) given that the patients in Cohort 2 are still in the treatment phase of the study. Consistent with results in ASHE patients, givosiran administration resulted in robust and durable lowering of ALA and PBG. In Cohort 1, givosiran administration resulted in meaningful reductions in the number and frequency of porphyria attacks. Specifically, as compared with the run-in phase, there was a 74 percent mean decrease in the annualized attack rate and a 75 percent mean reduction in annualized hemin administration. In addition, the maximum attack-free interval (i.e., the greatest period of time between porphyria attacks) was a mean of approximately 10.5 times that observed during the run-in phase. Favorable treatment effects in all three parameters were seen in each of the givosiran-treated patients. In contrast, the single placebo patient in Cohort 1 showed a generally similar number and frequency of porphyria attacks and a generally similar amount of hemin usage during the run-in and treatment phases. Finally, the aggregated blinded data for Cohort 2 patients, with approximately 3 months of treatment phase data, provided additional evidence of clinical activity. Specifically, as compared with the run-in phase, Cohort 2 patients receiving placebo or givosiran showed a 50 percent mean reduction in annualized attack rate and a 76 percent mean reduction in annualized hemin doses administered; the maximum attack-free interval was a mean of approximately 2.4 times that observed during the run-in phase. Results are provided in the table below.

Summary of Porphyria Attacks and Hemin Doses for Cohorts 1 and 2

Patient	Annualized Attack Number		Maximum Attack-Free Interval (Days)		Annualized Hemin Doses	
	Run-In Phase	Treatment Phase	Run-In Phase	Treatment Phase	Run-In Phase	Treatment Phase
COHORT 1						
Givosiran-1	38	14	10	42	102	19
Givosiran-2	47	15	6	62	55	29
Givosiran-3	35	2	10	169	44	2
Placebo	34	26	9	16	43	29
COHORT 2						
Aggregate Data*	17	9	23	56	15	4

* Cohort 2 remains blinded; data are for 84 days in the treatment phase and include combined results (N=4) for placebo and givosiran-treated patients

Safety Results

As of the data transfer on November 7, 2016, there were no drug-related serious adverse events (SAEs) reported in Cohorts 1-4. In Cohort 3, which remains blinded, one death was reported after the data transfer date due to acute pancreatitis, with evidence of sludge in the gallbladder, complicated by a pulmonary embolism and following an earlier hospitalization for bacteremia; the death was considered to be unlikely related to givosiran or placebo by the investigator and the study's Safety Review Committee. Of note, increases in pancreatic enzymes and acute pancreatitis have been reported in the literature in patients with acute hepatic porphyria (Shen *et al., Acta Neurol Taiwan,* 2008;17:177-183; Shiraki *et al., Nihon Rinsho,* 1995;53:1479-1483). In Cohorts 1 and 2, there were no discontinuations due to adverse events (AEs). Possibly or definitely related AEs reported in two or more cases were injection site reactions and myalgia; all of these events were mild. There were no other clinically significant changes in vital signs, electrocardiograms, clinical laboratory parameters, or physical examination.

To view the givosiran clinical results described in this press release, please visit www.alnylam.com/capella.

Conference Call Information

Alnylam management will discuss these clinical data in a webcast conference call tomorrow, Sunday, December 4, at 1:00 p.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 28671881. A replay of the call will be available beginning at 4:00 p.m. ET. To access the replay, please dial 855-859-2056 (domestic) or 404-537-3406 (international), and refer to conference ID 28671881.

About Givosiran

Alnylam is developing givosiran (formerly known as ALN-AS1), a subcutaneously administered, investigational RNAi

therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias, including acute intermittent porphyria (AIP). AIP is 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 aminolevulinic acid (ALA) and porphobilinogen (PBG). Patients with AIP can suffer from acute and/or recurrent life-threatening attacks characterized by severe abdominal pain, neuropathy (affecting the central, peripheral or autonomic nervous system), and neuropsychiatric manifestations. 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 prophylactic approach for the prevention of recurrent attacks, as well as for the treatment of acute porphyria attacks. Givosiran is an investigational compound, currently in early stage clinical development. The safety and efficacy of givosiran have not been evaluated by the U.S. Food and Drug Administration or any other health authority.

About Acute Hepatic Porphyrias
The porphyrias are a family of rare metabolic disorders with mostly autosomal dominant inheritance predominately 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). 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. 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. There are no approved therapeutics for prophylactic use (i.e., the prevention of acute attacks), although hemin is sometimes used in this manner in patients who experience recurrent attacks. 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 GalNAc Conjugates and Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugates
GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology enables subcutaneous dosing with increased potency and durability, and a wide therapeutic index. This delivery platform is being employed in nearly all of Alnylam's pipeline programs, including programs in clinical development.

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 is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines. Alnylam's pipeline of investigational RNAi therapeutics is focused in 3 Strategic Therapeutic Areas (STArs): Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics that address the major global health challenges of hepatic infectious diseases. In early 2015, Alnylam launched its "Alnylam 2020" guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, Alnylam expects to achieve a company profile with 3 marketed products, 10 RNAi therapeutic clinical programs - including 4 in late stages of development - across its 3 STArs. The company's demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Ionis, Novartis, Roche, Takeda, Merck, Monsanto, The Medicines Company, and Sanofi Genzyme. In addition, Alnylam holds an equity position in Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 200 peer-reviewed papers, including many in the

world's top scientific journals such as *Nature, Nature Medicine, Nature Biotechnology, Cell, New England Journal of Medicine,* and *The Lancet*. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information about Alnylam's pipeline of investigational RNAi therapeutics, please visit www.alnylam.com.

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 its STAr pipeline growth strategy, and 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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