September 7, 2017

Alnylam Provides Pipeline Update on Fitusiran and Givosiran Investigational RNAi Therapeutic Programs

- Company Suspends Fitusiran Dosing due to Thrombotic Event and Aims to Resume Dosing as Soon as Possible upon Agreement with Global Regulatory Authorities -

- Company Achieves Alignment with FDA on Givosiran Phase 3 Program Design, Including Interim Analysis Based on Reduction of Urinary Aminolevulinic Acid (ALA) as Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit -

- New Givosiran Phase 3 Plan Enables Potential for NDA Filing of Interim Analysis Results at or Around Year-End 2018 -

- Company to Host Conference Call Today at 8:00 a.m. ET, as well as Previously Scheduled RNAi Roundtable Webinar on Givosiran at 10:30 am ET -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (NASDAQ: ALNY), the leading RNAi therapeutics company, announced today an update on the company's fitusiran and givosiran investigational RNAi therapeutic programs. With fitusiran, an RNAi therapeutic in development for the treatment of hemophilia A and B with or without inhibitors, Alnylam is reporting a fatal thrombotic event in a patient with hemophilia A without inhibitors in the Phase 2 open-label extension (OLE) study of fitusiran. As a result, the Company has suspended dosing in all ongoing fitusiran studies pending further review of the safety event and development of a risk mitigation strategy. Based on overall consideration of fitusiran's benefit-risk profile, Alnylam is guiding that it aims to resume dosing as soon as possible upon agreement with global regulatory authorities and with appropriate protocol amendments in place for enhanced patient safety monitoring. With givosiran, an RNAi therapeutic in development for the treatment of acute hepatic porphyrias (AHP), Alnylam has reached alignment with the U.S. Food and Drug Administration (FDA) on a Phase 3 study design which includes an interim analysis based on reduction of a urinary biomarker, aminolevulinic acid (ALA), as a surrogate endpoint reasonably likely to predict clinical benefit. Based on the new givosiran Phase 3 design, the Company is now guiding that pending FDA review of the program at the time of interim analysis and assuming positive results, it expects to submit an NDA at or around year-end 2018.

Fitusiran Program Update

"We are deeply saddened to learn of this patient's death, and we extend our sympathies to his family," said Akshay Vaishnaw, M.D., Ph.D, Executive Vice President of R&D at Alnylam. "We believe that fitusiran holds great promise as a potential treatment option for patients with hemophilia, and we remain fully committed to its ongoing development. Following further investigation of this safety finding, implementation of a risk mitigation strategy, and alignment with global regulatory authorities, we expect to resume fitusiran dosing in our clinical studies as soon as possible, potentially as early as late 2017, with a goal of advancing this innovative investigational medicine to hemophilia patients in need."

Fitusiran clinical studies include the ongoing Phase 2 OLE study of hemophilia A and B patients with and without inhibitors and the ATLAS Phase 3 program, which has recently been initiated but in which patient dosing has yet to begin. Alnylam recently became aware of a fatal serious adverse event (SAE) that occurred in a patient with hemophilia A who was receiving fitusiran in the Phase 2 OLE study. Approximately nine days prior to hospital admission, he developed exercise-induced right hip pain that was treated with a total of three doses of factor VIII concentrate (31-46 IU/kg) on three separate days. Four days prior to admission, when the patient received his third dose of factor, he developed a severe headache. While he was initially suspected of having viral meningitis, the patient was diagnosed with subarachnoid hemorrhage on the basis of CT imaging, and treated with factor VIII concentrate administered two to three times daily. Over a 14-day hospitalization, his medical condition worsened despite the administration of factor and the patient died from subsequent cerebral edema. The initial diagnosis of subarachnoid hemorrhage was reported by the investigator as not related to fitusiran. For a more complete understanding, the Company initiated further investigation of the SAE, including review of the patient's CT scans by three independent neuro-radiologists, who all confirmed on September 1, 2017, that the initiating event was a cerebral venous sinus thrombosis, and not a subarachnoid hemorrhage. As a result of this new information, Alnylam suspended dosing in fitusiran studies in order to further investigate the safety event, now considered to be possibly related, and to develop a risk mitigation plan. The Company also notified study investigators and global regulatory authorities.

Based on today's program update, Alnylam will postpone its fitusiran RNAi Roundtable webinar previously scheduled for

September 12th until a later date.

Givosiran Program Update

"We believe that givosiran has shown very promising results as an innovative approach to potentially preventing debilitating and painful attacks in patients with acute hepatic porphyrias, a family of ultra-rare orphan diseases with enormous symptomatic burden and unmet need. Based on our ongoing clinical study results, we are very pleased with the support from global regulatory authorities who share our commitment to evaluate and establish the efficacy and safety of givosiran as a therapeutic option for patients as rapidly as possible," said Jeff Miller, General Manager of the givosiran program. "We have now reached alignment with the FDA on a Phase 3 program that includes an interim analysis based on reduction of urinary levels of ALA, a biomarker that the FDA considers to be reasonably likely to predict clinical benefit. Based on this new design, Alnylam now expects - pending FDA review of the program at the time of the interim analysis and assuming positive results - to be in a position to submit an NDA at or around year-end 2018, which represents a significant acceleration in our efforts to bring this investigational medicine to patients."

In interim Phase 1 study results presented at the 2017 International Congress on Porphyrins and Porphyrias (ICPP) from a randomized, double-blind, placebo-controlled study in patients with acute intermittent porphyria (AIP), givosiran demonstrated an over 80 percent mean reduction of urinary ALA and an over 70 percent mean decrease relative to placebo in the estimated annualized number of porphyria attacks requiring treatment at a healthcare facility or with intravenous hemin administration. Excluding porphyria attacks, three patients had four SAEs, including one previously reported fatal episode of hemorrhagic pancreatitis; none of these SAEs were assessed as related to study drug. Based on these results, givosiran received PRIME designation by the European Medicines Agency (EMA) and Breakthrough Therapy Designation by the FDA. The Company has achieved alignment with the FDA on a randomized, double-blind, placebo-controlled Phase 3 study design that includes an interim analysis with reduction in urinary levels of ALA at three months of treatment as a biomarker that is reasonably likely to predict clinical benefit; discussions with other global regulatory authorities are ongoing. Alnylam expects to initiate a Phase 3 study of givosiran in late 2017 with interim analysis data available in mid-2018.

As previously scheduled, Alnylam will discuss the givosiran program, including the Phase 3 study and interim analysis design, at an RNAi Roundtable event today at 10:30 a.m. ET. This event will be webcast live on the Investors page of the Alnylam website, www.alnylam.com, and a replay will be posted approximately three hours after the event.

Conference Call Details

Management will discuss these updates via conference call today, Thursday, September 7, 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 81805520. A replay of the call will be available beginning at 11:00 a.m. ET on September 7, 2017. To access the replay, please dial 855-859-2056 (domestic) or 404-537-3406 (international), and refer to conference ID 81805520.

About Fitusiran

Fitusiran is an investigational, once-monthly, subcutaneously administered RNAi therapeutic targeting antithrombin (AT) for the treatment of hemophilia A and B, with and without inhibitors. Fitusiran also has the potential to be used for rare bleeding disorders. Fitusiran is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding. Fitusiran utilizes Alnylam's ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability. The clinical significance of this technology is under investigation.

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

About Hemophilia

Hemophilia is a hereditary bleeding disorder characterized by an underlying defect in the ability to generate adequate levels of thrombin needed for effective clotting, thereby resulting in recurrent bleeds into joints, muscles, and major internal organs. There are approximately 200,000 persons diagnosed worldwide with hemophilia A and hemophilia B.

Standard treatment for persons with hemophilia currently involves replacement of the deficient clotting factor either as prophylaxis or "on-demand" therapy, which can lead to a temporary restoration of thrombin generation capacity. However, as many as one third of people with severe hemophilia A will develop a neutralizing antibody to their replacement factor - a very serious complication; individuals with these 'inhibitors' become refractory to standard replacement factor therapy.

Inhibitors may also develop in severe Hemophilia B patients, albeit at a lower rate.

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 been granted the following regulatory designations: PRIME by European Medicines Agency (EMA), Breakthrough Designation by the U.S. Food and Drug Administration (FDA) and Orphan Drug Designation by both EMA and FDA for the treatment of AHP.

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.

Alnylam - Sanofi Genzyme Alliance

In January 2014, Alnylam and Sanofi Genzyme, the specialty care global business unit of Sanofi, formed an alliance to accelerate the advancement of RNAi therapeutics as a potential new class of innovative medicines for patients around the world with rare genetic diseases. The alliance enables Sanofi Genzyme to expand its rare disease pipeline with Alnylam's novel RNAi technology and provides access to Alnylam's R&D engine, while Alnylam benefits from Sanofi Genzyme's proven global capabilities to advance late-stage development and, upon commercialization, accelerate market access for these promising genetic medicine products.

In November 2016, Sanofi Genzyme elected to co-develop (through Sanofi R&D) and co-commercialize fitusiran in the United States, Canada and Western Europe, in addition to commercializing fitusiran in its rest of world territories.

About RNAi

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding protein synthesis 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, with the goal of preventing disease-causing proteins from being made.

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 planned interactions with regulatory authorities and the expected resumption of dosing in its fitusiran clinical studies, the potential for fitusiran for the treatment of patients with hemophilia A and B, with or without inhibitors, the potential for givosiran for the treatment of hepatic porphyrias, expectations regarding the initiation of a Phase 3 clinical study for givosiran and the possibility of an interim analysis in such study, the anticipated filing date of an NDA for givosiran, 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 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.

Fitusiran and givosiran have 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 the safety or effectiveness of these investigational therapeutics.

View source version on businesswire.com: http://www.businesswire.com/news/home/20170907005750/en/

Alnylam Pharmaceuticals, Inc.
Investors and Media
Christine Regan Lindenboom, 617-682-4340
or
Investors
Josh Brodsky, 617-551-8276

Source: Alnylam Pharmaceuticals, Inc.