Alnylam Announces Plan to Initiate Rolling Submission of a New Drug Application and Pursue Full Approval for Givosiran

October 15, 2018

− Topline Results on Primary Endpoint of Annualized Attack Rate Expected in Early 2019 –

− Company Plans to Initiate a Rolling Submission of an NDA in 2018 with Addition of Full Clinical Results in Mid-2019 in Support of a Full Approval –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 15, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that in consultation with the U.S. Food and Drug Administration (FDA), the Company plans to pursue a full approval based on the complete results of the ENVISION Phase 3 study of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyria (AHP), rather than filing based on the interim Phase 3 results. The FDA has also agreed to a rolling submission of a New Drug Application (NDA), which will be initiated in 2018 with full clinical sections submitted in mid-2019, assuming positive study results.

"The AHPs are devastating diseases and our goal is to help address the significant unmet need that exists today for people living with AHP. Based on our positive Phase 1/2 clinical results presented earlier this year and the positive interim analysis results from the ENVISION Phase 3 trial, we're encouraged by givosiran's potential to make a difference in the lives of AHP patients," said Akin Akinc, Ph.D., Vice President and General Manager, Givosiran Program at Alnylam. "Our constructive discussions with the FDA led to our decision to pursue a full approval path with complete ENVISION study results, including porphyria attack data, which are expected much earlier than originally planned. The FDA has also agreed to a rolling submission of the NDA which will begin this year. This filing plan creates the potential to achieve full approval as rapidly as possible and aligns with our strategy in all other countries."

Alnylam previously reported positive topline results from the interim analysis of the ENVISION Phase 3 study of givosiran demonstrating a statistically significant reduction (p less than 0.001) in urinary ALA levels, a surrogate biomarker that is reasonably likely to predict clinical benefit. As previously reported, serious adverse events (SAEs) were reported in 22 percent (5/23) of givosiran patients and 10 percent (2/20) of placebo patients in the interim analysis cohort of 43 patients, with one patient (4 percent) on givosiran discontinuing treatment due to an increase in liver transaminase that resolved.

Alnylam continues to dose patients in the ongoing ENVISION study, where enrollment was completed ahead of schedule with 94 AHP patients. The Company expects to report topline full study results of the primary endpoint – the annualized attack rate after six months of treatment – in early 2019. As previously guided, the Company intends to file for marketing authorization in all other markets based on the complete results of the ENVISION Phase 3 study, assuming positive results.

About the ENVISION Phase 3 Study
The ENVISION Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of AHPs. Patients were randomized on a 1:1 basis to receive 2.5 mg/kg of givosiran or placebo subcutaneously administered monthly, over a six-month treatment period. The primary endpoint is the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit or hemin administration at home over the six-month treatment period. The interim analysis included 43 AHP patients who were on study for at least three months and evaluated reduction of a urinary biomarker – ALA – in 41 patients with AIP, as a surrogate endpoint reasonably likely to predict clinical benefit. Key secondary and exploratory endpoints will evaluate reductions in the hallmark symptoms of AHPs, such as pain, nausea, and fatigue, as well as impact on quality of life.

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. 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 an AHP are often misdiagnosed or remain undiagnosed for an average of 15 years. Currently, there are no treatments approved to prevent debilitating attacks and treat the chronic symptoms 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 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 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 improve the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS) 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. ONPATTRO™ (patisiran) lipid complex injection, available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults, is Alnylam’s first U.S. FDA-approved RNAi therapeutic. In the EU, ONPATTRO is approved for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including three 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 worldwide 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 the potential benefits of givosiran, plans to initiate a rolling NDA submission in 2018 and pursue a full approval in 2019 based on the complete results of the ENVISION Phase 3 study of givosiran in the U.S. and plans to file marketing approval in all other territories, the expected timing of the report of topline full results from the ENVISION study, 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, 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.

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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20181015005273/en/

Source: Alnylam Pharmaceuticals, Inc.

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