Alnylam Announces Positive Topline Results from Interim Analysis of ENVISION Phase 3 Study of Givosiran in Patients with Acute Hepatic Porphyria

September 27, 2018

− Givosiran Treatment Resulted in Significant Reduction of Urinary Aminolevulinic Acid (ALA), a Disease Biomarker Reasonably Likely to Predict Clinical Benefit –

− Company Plans to Discuss Results with FDA Regarding a Potential NDA Filing at or Around Year-End in Support of an Accelerated Approval –

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

− Alnylam to Host Conference Call Today at 8:00 am ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 27, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today positive topline results from the interim analysis 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). The pre-specified interim analysis was based on lowering of urinary ALA levels as a surrogate biomarker that is reasonably likely to predict clinical benefit.

Results of the interim analysis showed that givosiran treatment was associated with a statistically significant reduction in urinary ALA levels in acute intermittent porphyria (AIP) patients, relative to placebo (p less than 0.001). The Company plans to discuss these data and the regulatory path forward with the FDA, and, pending the outcome of those discussions, intends to file a New Drug Application (NDA) at or around year-end 2018 in support of a potential Accelerated Approval. The interim analysis had a data cut-off date of August 22, 2018 and included 43 patients with AHPs (41 patients with AIP, one with variegate porphyria [VP], and one with hereditary coproporphyria [HCP]) who were on study for at least three months. As of the data cut-off date, there were no deaths, and serious adverse events (SAEs) were reported in 22 percent (5/23) of givosiran patients and 10 percent (2/20) of placebo patients. One patient (4 percent) on givosiran discontinued treatment due to an increase in liver transaminase – which resolved – that was greater than eight times the upper limit of normal (ULN), a protocol-defined stopping rule. There were no treatment discontinuations in the placebo group.

“The AHPs are devastating diseases in which patients suffer from both debilitating neurovisceral attacks as well as chronic pain and fatigue. We are pleased and encouraged that the interim analysis of the ENVISION Phase 3 study demonstrated that givosiran treatment was associated with statistically significant lowering of ALA, a disease biomarker reasonably likely to predict clinical benefit,” said Akshay Vaishnaw, M.D., Ph.D., President of Research and Development at Alnylam. “With these interim results in hand, we plan to meet with the FDA to discuss the results and the overall benefit-risk profile for a potential NDA submission at or around year-end in support of an Accelerated Approval. In the meantime, with enrollment in ENVISION completed ahead of schedule, we look forward to reporting topline results for the full study early next year. If clinical efficacy and acceptable safety are confirmed in the full study, we believe givosiran has the potential to transform the lives of patients living with an AHP.”

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.

Conference Call Details

Alnylam management will discuss the ENVISION interim analysis results via conference call today, September 27, 2018, at 8:00 am ET. A webcast presentation will also be available on the Investors page of the Company’s website, www.alnylam.com. To access the call, please dial (800) 682-0995 (domestic) or (334) 323-0505 (international) five minutes prior to the start time and refer to conference ID 9024965. A replay of the call will be available beginning at 11:00 am ET on September 27, 2018. To access the replay, please dial (888) 203-1112 (domestic) or (719) 457-0820 (international) and refer to conference ID 9024965.

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 6-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 6-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 discuss the results from the ENVISION interim analysis and overall benefit-risk profile of givosiran and the regulatory path forward with the FDA, the timing for a potential filing of an NDA in support of a possible Accelerated Approval, the expected timing of the report of topline 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/20180927005235/en/

Source: Alnylam Pharmaceuticals, Inc.

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