# Alnylam Reports Positive Topline Results from HELIOS-A Phase 3 Study of Vutrisiran in Patients with hATTR Amyloidosis with Polyneuropathy

Jan 07, 2021

*– Vutrisiran Met Primary and All Secondary Endpoints at 9 Months, with Statistically Significant Improvements in Progression of Neuropathy, Quality of Life (QOL), and Gait Speed, Relative to Placebo –*

*– Majority of Patients Showed Reversal of Disease Manifestations with Improvements in Neuropathy Impairment and QOL, Relative to Baseline –*

*– Vutrisiran Showed Improvements in the 9-Month Exploratory Cardiac Endpoint of NT-proBNP, Relative to Placebo –*

*– In Addition, Vutrisiran Demonstrated Encouraging Safety and Tolerability Profile –*

*– Alnylam Intends to Present Full 9-Month Results and File New Drug Application (NDA) in Early 2021 –*

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

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 7, 2021-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com%2F&esheet=52357744&newsitemid=20210107005224&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=4c9201df548a47b47ba6762dd7f88a33) (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the HELIOS-A Phase 3 study of vutrisiran, an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis, met its primary and both secondary endpoints at nine months in patients with hATTR amyloidosis with polyneuropathy. The primary endpoint was the change from baseline in the modified Neuropathy Impairment Score (mNIS+7) at 9 months as compared to historical placebo data from the APOLLO Phase 3 study of patisiran. The two secondary endpoints were changes in quality of life assessed by the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and gait speed assessed by the timed 10-meter walk test (10-MWT) compared to historical placebo. Vutrisiran met the primary endpoint (p less than 0.001) and achieved statistically significant results (p less than 0.001) for each of the Norfolk QoL-DN and 10-MWT secondary endpoints. In addition, vutrisiran treatment showed improvement compared to placebo on the exploratory cardiac biomarker endpoint, NT-proBNP (nominal p less than 0.05). Vutrisiran also demonstrated an encouraging safety and tolerability profile.

Based on these positive results, the Company plans to submit a New Drug Application (NDA) for vutrisiran with the U.S. Food and Drug Administration (FDA) in early 2021, and to follow with regulatory filings in additional countries, such as Brazil and Japan. The Company plans to submit a Marketing Authorisation Application (MAA) in the EU upon obtaining the results of the 18-month analysis – expected in late 2021 – as previously aligned with the European Medicines Agency (EMA).

“We are excited to report positive topline results from the HELIOS-A study, which show that vutrisiran reduces neurologic impairment and improves quality of life in patients with hATTR amyloidosis with polyneuropathy as soon as 9 months, with an encouraging safety and tolerability profile. In addition, we’re very pleased to see evidence for reversal of polyneuropathy manifestations of disease and also favorable effects on the exploratory cardiac endpoint, NT-proBNP. We believe that vutrisiran, as a low-dose, once-quarterly,

subcutaneously administered therapy, has the potential to be a highly attractive therapeutic option for patients living with this progressive, life-threatening, multi-system disease. We look forward to presenting the full 9-month results from HELIOS-A at a medical meeting in early 2021 and to announcing additional 18-month results, including additional exploratory cardiac endpoint data, in late 2021," said Akshay Vaishnaw, M.D., Ph.D., President of R&D at Alnylam. "We would like to recognize and extend our profound gratitude to the patients, caregivers, investigators, and study staff who are participating in HELIOS-A and who, through their commitment during an especially difficult year, have helped make possible another potential advancement in the treatment of hATTR amyloidosis with polyneuropathy. We look forward to initiating our regulatory filings in early 2021 as we work to bring this investigational treatment one step closer to patients with this rare disease."

HELIOS-A (NCT03759379) is a Phase 3 global, randomized, open-label study to evaluate the efficacy and safety of vutrisiran. The study enrolled 164 patients with hATTR amyloidosis with polyneuropathy at 57 sites in 22 countries. Patients were randomized 3:1 to receive either 25mg of vutrisiran (N=122) via subcutaneous injection once every three months or 0.3 mg/kg of patisiran (N=42) via intravenous infusion once every three weeks (as a reference comparator) for 18 months. The primary endpoint is the change from baseline in mNIS+7 score at 9 months[1], relative to historical placebo. Secondary endpoints at 9 months are the change from baseline in the Norfolk QoL-DN score and the timed 10-MWT, relative to historical placebo. Changes from baseline in NT-proBNP were evaluated as an exploratory endpoint at 9 months. The efficacy results of vutrisiran in HELIOS-A are compared to historical placebo control data from the landmark APOLLO Phase 3 study, which evaluated the efficacy and safety of patisiran in a patient population similar to that studied in HELIOS-A. Additional secondary endpoints at 18 months will be evaluated in the HELIOS-A study, including change from baseline in mNIS+7, Norfolk QoL-DN, 10-MWT, modified body mass index (mBMI), Rasch-built Overall Disability Scale (R-ODS), and serum transthyretin (TTR) levels. Additional exploratory cardiac endpoint data at the 18-month time point will be evaluated, including NT-proBNP, echocardiographic measures and cardiac amyloid assessments with technetium scintigraphy imaging. Following the 18-month study period, all patients are eligible to receive vutrisiran for an additional 18 months as part of an open-label extension study. Full 9-month results will be presented at a medical conference in early 2021 and topline 18-month results, including further exploratory cardiac endpoint data, are expected to be announced in late 2021.

Vutrisiran demonstrated an encouraging safety profile. There were two study discontinuations (1.6 percent) due to adverse events in the vutrisiran arm by Month 9, both due to deaths, neither of which was considered related to study drug. There were two serious adverse events (SAEs) deemed related to vutrisiran by the study investigator, consisting of dyslipidemia and urinary tract infection. Treatment emergent adverse events (AEs) occurring in 10 percent or more patients included diarrhea, pain in extremity, fall and urinary tract infections, with each of

these events occurring at a similar or lower rate as compared with historical placebo. Injection site reactions (ISRs) were reported in five patients (4.1 percent) and were all mild and transient. There were no clinically significant changes in liver function tests (LFTs).

“The HELIOS-A results reinforce our commitment to building an industry-leading franchise of medicines for the treatment of ATTR amyloidosis which began with the development and approval of ONPATTRO as a treatment for patients with hATTR amyloidosis with polyneuropathy. Indeed, the vutrisiran results from HELIOS-A now serve as a second example of the potential for RNAi therapeutics to have a meaningful impact for patients, showing the ability to halt and potentially even reverse polyneuropathy manifestations of the disease. Furthermore, our robust development program, including the APOLLO-B and HELIOS-B studies, investigates the potential of patisiran and vutrisiran, respectively, to treat the cardiac manifestations of disease across a broad spectrum of patients with ATTR amyloidosis,” said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. “We believe that our ATTR amyloidosis franchise will be a significant driver of Alnylam’s growth in the years to come, with the potential to position Alnylam as a top tier biopharma company.”

Vutrisiran has been granted Orphan Drug Designation in the United States and the European Union for the treatment of ATTR amyloidosis. Vutrisiran has also been granted a Fast Track designation in the United States for the treatment of the polyneuropathy of hATTR amyloidosis in adults. The safety and efficacy of vutrisiran are being evaluated in the comprehensive HELIOS clinical development program and have not yet been evaluated by any health authority. The ongoing HELIOS-B Phase 3 clinical trial in patients with ATTR amyloidosis with cardiomyopathy was initiated in late 2019 and is currently enrolling at sites around the world. Together, the HELIOS-A and -B studies are intended to demonstrate the broad impact of vutrisiran across the multisystem manifestations of disease and the full spectrum of patients with ATTR amyloidosis.

## Conference Call Information

Alnylam management will discuss the HELIOS-A results via conference call on Thursday, January 7, 2021, at 8:00 am ET. A webcast presentation will also be available on the Investors page of the Company’s website, www.alnylam.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52357744&newsitemid=20210107005224&lan=en-US&anchor=www.alnylam.com&index=2&md5=995027755812401275f13a92c68f1e04). To access the call, please dial 877-312-7507 (domestic) or +1-631-813-4828 (international) five minutes prior to the start time and refer to conference ID 4398564. A replay of the call will be available beginning at 11:00 am ET on the day of the call. To access the replay, please dial 855-859-2056 (domestic) or +1-404-537-3406 (international) and refer to conference ID 4398564.

## About hATTR Amyloidosis

Hereditary transthyretin (TTR)-mediated amyloidosis (hATTR) is an inherited, progressively debilitating, and often fatal disease caused by mutations in the TTR gene. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. Mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissue, such as the peripheral nerves and heart, resulting in intractable peripheral sensory-motor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. hATTR amyloidosis, represents a major unmet medical need with significant morbidity and mortality affecting approximately 50,000 people worldwide. The median survival is 4.7 years following diagnosis, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy.

## About Vutrisiran

Vutrisiran is an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of ATTR amyloidosis, which encompasses both hereditary (hATTR) and wild-type (wtATTR) amyloidosis. It is designed to target and silence specific messenger RNA, blocking the production of wild-type and variant transthyretin (TTR) protein before it is made. Quarterly administration of vutrisiran may help to reduce deposition and facilitate the clearance of TTR amyloid deposits in tissues and potentially restore function to these tissues. Vutrisiran utilizes Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform, designed for increased potency and high metabolic stability that allows for infrequent subcutaneous injections. The safety and efficacy of vutrisiran have not been evaluated by the U.S. Food and Drug Administration, European Medicines Agency 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 whole new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS)/ocular

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 RNAi therapeutics platform. Alnylam's commercial RNAi therapeutic products are ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran), and, in Europe, Leqvio® (inclisiran). Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam exceeded the goals first established in 2015 under 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 is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=52357744&newsitemid=20210107005224&lan=en-US&anchor=www.alnylam.com&index=3&md5=fbd8e185d549920b00986a8004bd2e26) and engage with us on Twitter at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2Falnylam&esheet=52357744&newsitemid=20210107005224&lan=en-US&anchor=%40Alnylam&index=4&md5=2cec3d5ef73f1f53e04a758b0ae0d3ab) or on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=52357744&newsitemid=20210107005224&lan=en-US&anchor=LinkedIn&index=5&md5=4937ec048447b399b1e89eaab086b9dc).

## Alnylam Forward Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, expectations regarding the direct or indirect effects on Alnylam's business, activities and prospects as a result of the COVID-19 pandemic, or delays or interruptions resulting therefrom and the success of Alnylam's mitigation efforts, Alnylam's views and plans with respect to the potential for RNAi therapeutics, including vutrisiran and patisiran, expectations regarding the safety and efficacy of vutrisiran as a treatment for hATTR amyloidosis with polyneuropathy, and its potential to have a meaningful impact on the course of this disease, expectations regarding the potential of vutrisiran and patisiran to treat the cardiac manifestations of ATTR amyloidosis across a broad spectrum of patients, Alnylam's prospects for building an industry-leading ATTR amyloidosis franchise and to become a top-tier biopharma company, the expected timing for the filing of regulatory submissions for vutrisiran the presentation of full 9-month results and the announcement of 18-month topline results, including exploratory cardiac endpoint data, 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, the availability of safe and effective vaccine(s), material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by Alnylam products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to Alnylam's business, the effectiveness or timeliness of steps taken by Alnylam to mitigate the impact of the pandemic, and Alnylam's ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates, including vutrisiran; 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 or its or its partner Novartis' marketed products, including ONPATTRO, GIVLAARI, OXLUMO and Leqvio (in Europe); obtaining, maintaining and protecting intellectual property; intellectual property matters including potential patent litigation relating to its platform, products or product candidates; obtaining regulatory approval for its product candidates, including vutrisiran, and the success of its partner Novartis', in obtaining regulatory approval for inclisiran in the U.S. and elsewhere, and maintaining regulatory approval and obtaining pricing and reimbursement for its products, including ONPATTRO, GIVLAARI, and OXLUMO, as well as its partner Novartis' success obtaining pricing and reimbursement for Leqvio; progress in continuing to establish an ex-United States infrastructure; successfully launching, marketing and selling its approved products globally, including ONPATTRO, GIVLAARI, and OXLUMO, and achieving net product revenues for ONPATTRO within its revised expected range during 2020; 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 within the ranges of guidance provided by Alnylam through the implementation of further discipline in operations to moderate spend and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to establish and maintain strategic business alliances and new business initiatives; Alnylam's dependence on third parties, including Novartis for the continued development and commercialization of Leqvio, Regeneron for development, manufacture and distribution of certain products, including eye and CNS products, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; 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.

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[1] In alignment with the EMA, the primary endpoint of change from baseline in mNIS+7 will be evaluated at 18 months to support an MAA.

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