Alnylam Announces New Advances in ATTR Amyloidosis Program

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− Initiates Clinical Study of Biannual Dosing Regimen of Investigational Vutrisiran in hATTR Patients with Polyneuropathy, with Data Expected in 2022 Potentially Supporting sNDA Submission –

− Introduces New ATTR Program Aimed at Achieving Annual Dosing Regimen with Highly Potent and Reversible Effects; Expected IND Filing at or Around Year-end 2022 –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--May 11, 2021-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that it has started a clinical study of a biannual dosing regimen of vutrisiran, an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis. The study is being conducted during a randomized treatment extension (RTE) period in the HELIOS-A Phase 3 study, and will characterize the safety, efficacy, and TTR reduction of a 50 mg biannual dosing regimen of subcutaneously administered vutrisiran in patients with hereditary ATTR (hATTR) amyloidosis with polyneuropathy. In addition, the Company announces today advancement of a new pre-clinical ATTR amyloidosis program aimed at achieving highly potent and reversible TTR reduction of over 90 percent with an annual subcutaneous dosing regimen.

“Alnylam has a long-standing commitment to continuous innovation aimed at providing breakthrough treatment options for patients with ATTR amyloidosis. We’re pleased to have now initiated a clinical study of a biannual dosing regimen for vutrisiran. If shown to be safe and efficacious, the new dosing regimen may provide some patients with a treatment option that neatly aligns the frequency of administration with biannual visits to their doctor,” said Rena Denoncourt, Vice President, Vutrisiran Program Leader. “In addition, based on continued discoveries from our RNAi therapeutics platform, we’re also advancing a new pre-clinical program that could enable highly potent and reversible TTR reduction with an annual dosing regimen. We believe that once yearly dosing could provide a vaccine-like dosing schedule strategy for management of ATTR amyloidosis, providing meaningful life-cycle management for our ATTR franchise.”

As reported previously, positive results were achieved in HELIOS-A with a 25 mg quarterly dosing regimen of subcutaneously administered vutrisiran; a New Drug Application (NDA) for the approval of vutrisiran was filed with the U.S. Food and Drug Administration (FDA) in April 2021 for the treatment of the polyneuropathy of hATTR amyloidosis in adults[1]. The vutrisiran biannual dosing study is being conducted as part of the HELIOS-A randomized, open-label study. During the RTE period, which begins following completion of the 18-month HELIOS-A treatment period, patients are randomized 1:1 to receive 25 mg of vutrisiran quarterly or 50 mg of vutrisiran biannually for the remainder of the study. Patients will undergo periodic assessments for safety and TTR reduction, and efficacy assessments at months nine and 18 of the RTE. As previously disclosed in mid-2020, clinical pharmacology data indicate that a 50 mg biannual dose of vutrisiran is expected to achieve comparable TTR reduction – over 80 percent – to that demonstrated with the 25 mg quarterly dosing regimen of vutrisiran. Alnylam expects results from the RTE study in 2022; if positive, data would support a supplemental NDA (sNDA) submission to the FDA.

The new ATTR program announced today stems from continued innovation from Alnylam’s RNAi therapeutics platform efforts. Specifically, Alnylam scientists have developed an extended duration platform, called IKARIA™, that is aimed at highly potent (>90 percent) target mRNA silencing with an annual dosing regimen. Targeting mRNA with the IKARIA platform is expected to yield small interfering RNA (siRNA) with potentially long-acting and reversible effects and a proven RNAi mechanism of action. This new platform has yielded ALN-TTRsc04, which is planned to enter clinical development at or around year-end 2022 with an investigational new drug (IND) application filing. If successfully developed, ALN-TTRsc04 is expected to have minimal, if any, third-party royalty obligations. Alnylam plans to present data from its IKARIA platform and ALN-TTRsc04 program at a scientific meeting in mid-2021.

“Our platform team continues to discover innovations for RNAi therapeutics that we believe can deliver meaningful advances for patients. Our new IKARIA platform represents an excellent example,” said Kevin Fitzgerald, Ph.D., Senior Vice President, Chief Scientific Officer. “With IKARIA, we are confident we can design long-acting siRNA with all the proven pharmacological advantages and established human experience of RNAi therapeutics, including predictable dose-dependence and onset/offset kinetics, without permanent effects on the target or cell.”

About HELIOS-A Phase 3 Study

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 nine months, relative to an external placebo group (APOLLO). Secondary endpoints at 9 months are the change from baseline in the Norfolk QoL-DN score and the timed 10-MWT, relative to an external placebo group. Changes from baseline in NT-proBNP were evaluated as an exploratory endpoint at nine months. The efficacy results of vutrisiran in HELIOS-A are compared to the placebo group 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 treatment period, all patients are eligible to receive vutrisiran for an additional 18 months as part of the randomized treatment extension.

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 may allow 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 hATTR Amyloidosis

Hereditary transthyretin (TTR)-mediated amyloidosis (hATTR) is an inherited, progressively debilitating, and fatal disease caused by variants (i.e., mutations) in the TTR gene. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. Variants 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 IKARIA™ Platform

Alnylam's IKARIA platform takes advantage of more than two decades of experience in developing RNAi therapeutics. IKARIA enables an extended duration of activity in preclinical studies, with potential for annual dosing in humans, and has design features which provide exquisite specificity, further widening the potential therapeutic index, with enhanced target reduction levels.

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 Leqvio® (inclisiran) being developed and commercialized by Alnylam's partner Novartis. Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam is executing on its "Alnylam P ^{5}x25" strategy to deliver transformative medicines in both rare and common diseases benefiting patients around the world through sustainable innovation and exceptional financial performance, resulting in a leading biotech profile. Alnylam 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, on LinkedIn, or on Instagram.

Alnylam Forward Looking Statements

Various statements in this release concerning Alnylam's expectations, plans, aspirations, and goals, including those related to vutrisiran and its potential as a low-dose, once quarterly, subcutaneously administered treatment option with an encouraging safety profile for patients with hATTR amyloidosis with polyneuropathy, the potential of a new biannual dosing regimen of vutrisiran for such patients, the expected timing of additional data on the biannual dosing regimen and potential additional regulatory filings for vutrisiran, including an sNDA with the FDA, if the data for such biannual dosing are positive, the potential of the IKARIA platform to enable highly potent (>90 percent) target mRNA silencing with an annual dosing regimen and the expected timing for the initiation of clinical studies for ALN-TTRsc04, that could enable highly potent and reversible TTR reduction with an annual dosing regimen and, if successful, could provide a vaccine-like strategy for management of ATTR amyloidosis, becoming a leading biotech company, and the achievement of its "Alnylam P ^{5}x25" strategy, 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 on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam's efforts to mitigate the impact of the 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; the pre-clinical and clinical results for its product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling its approved products globally; delays, interruptions or failures in the manufacture and supply of its product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication for ONPATTRO (or vutrisiran, if approved) in the future; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Novartis, Regeneron and Vir; 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 its other SEC filings. 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.

This release is not intended to convey conclusions about efficacy or safety as to any investigational uses or dosing regimens of any investigational RNAi therapeutics. There is no guarantee that any investigational therapeutics or dosing regimens for such therapeutics will successfully complete clinical development or gain health authority approval.

[1] The safety and efficacy of investigational vutrisiran have not been evaluated by the U.S. Food and Drug Administration, European Medicines Agency, or any other health authority. Regulatory authorities have not yet determined that vutrisiran is safe or effective for any indication.

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