Alnylam Announces 2021 Product and Pipeline Goals and Provides Program Updates at R&D Day

December 15, 2020

− Product and Pipeline Goals Include Execution on Four Commercial Brands, One New NDA Filing, Two Phase 3 Data Readouts, Amongst Other Milestones –

– New Clinical Data Presented from Phase 1 Monotherapy Study of ALN-AGT Show Mean Reduction in 24-Hour Systolic Blood Pressure of Over 15 mm Hg –

– New Highlighted Programs Include Investigational RNAi Therapeutics for Recurrent Renal Stones, Non-alcoholic Steatohepatitis (NASH), Gout, Metabolic Syndrome, and Type 2 Diabetes, Expanding RNAi Opportunities into Specialty and Prevalent Disease Markets –

– Continued Progress in Extrahepatic Delivery Supports Pipeline Advancement in CNS, Ocular, and Pulmonary Diseases, with Initial Program Reaching Clinical Development Stage in 2021 –

– Alnylam to Webcast its R&D Day Event Today and Tomorrow at 9:00 a.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Dec. 15, 2020-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, is kicking off a virtual R&D Day event today. During the two-day event, the Company plans to showcase its commercial and R&D progress, including its product and pipeline goals for 2021, focused on continued commercial execution and advancement of early-, mid- and late-stage investigational programs. Alnylam will also provide an update on its progress toward achieving a self-sustainable financial profile for future growth and value creation.

“Five years ago, we charted our *Alnylam 2020* goals of building a multi-product, global commercial company with a deep clinical pipeline for future growth and an organic product engine for sustainable innovation. We have now exceeded those ambitious goals with four marketed products and 12 organically derived clinical programs across four strategic therapeutic areas,” said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. “In 2021, across our portfolio of partnered and proprietary programs, we aim to deliver performance on four commercial brands, file one new NDA, and report topline results on two Phase 3 programs, amongst other objectives. In the coming years, we believe Alnylam is positioned to emerge as a leading, top-five biotech company, driven by continuous global commercial execution and top-line growth, advancement of a robust clinical development pipeline, continued leverage of our organic product engine as a source of sustainable innovation and transformational medicines, and achievement of a self-sustainable financial profile.”

2021 Product and Pipeline Goals

ONPATTRO® (patisiran), a commercial-stage RNAi therapeutic targeting transthyretin (TTR) for the treatment of polyneuropathy in patients with hATTR amyloidosis. Alnylam plans to:

- Continue global commercial execution
- Complete enrollment in the APOLLO-B study, which is now expected in early 2021

GIVLAARI® (givosiran), a commercial-stage RNAi therapeutic for the treatment of adults with acute hepatic porphyria (AHP). Alnylam plans to:

- Continue global commercial execution
- Achieve regulatory approval of GIVLAARI in Japan in mid-2021

OXLUMO™ (lumasiran), a commercial-stage RNAi therapeutic for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients. Alnylam plans to:

- Execute on global commercial launches throughout 2021
- Achieve regulatory approval of OXLUMO in Brazil in early 2021
- Report topline results from the ILLUMINATE-C Phase 3 study in mid-2021

Vutrisiran, an investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis. Alnylam plans to:

- Report topline results from the HELIOS-A Phase 3 study (9-month endpoint) in early 2021
- File a New Drug Application (NDA) with the FDA in early 2021, assuming positive results from the HELIOS-A Phase 3 study
- Initiate data generation in early 2021 to support a biannual dose regimen of vutrisiran
- Report topline results from the HELIOS-A Phase 3 study (18-month endpoint, including cardiac data) in late 2021
- Continue enrollment in the HELIOS-B Phase 3 study throughout 2021

ALN-AGT, an investigational RNAi therapeutic in development for the treatment of hypertension. Alnylam plans to:

- Initiate the KARDIA Phase 2 studies in mid-2021

Alnylam also plans to support, as needed, Novartis’ continued efforts with respect to **Leqvio® (inclisiran)**, the first and only siRNA therapy (or RNAi

therapeutic) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, now approved in Europe. Approval of inclisiran by the FDA is anticipated by end of 2020, and Novartis plans to:

- Execute on global commercial launches throughout 2021
- Continue enrollment in the ORION-4 Phase 3 cardiovascular outcomes (CVOT) study in 2021

Alnylam also plans to support, as needed, Sanofi's continued efforts in advancing **fitusiran**, an investigational RNAi therapeutic in development for the treatment of hemophilia, for which Sanofi intends to resume dosing in the ATLAS Phase 3 studies.

In addition, the Company plans to continue advancement of its additional mid- and early-stage clinical pipeline programs.

"At Alnylam, we are excited about the opportunity for RNAi therapeutics in rare and common diseases with liver and extra-hepatic delivery to realize the greatest potential for this new class of medicines in human health," said Akshay Vaishnaw, M.D., Ph.D., President of R&D at Alnylam. "Our annual R&D Day will feature updates across our pipeline, including deep dive discussions on RNAi therapeutic opportunities in wild-type ATTR amyloidosis, hypertension, and NASH. Notably, new data from our ALN-AGT program, with an over 15 mm Hg mean reduction in systolic blood pressure as monotherapy, highlight the opportunity to reimagine the management of hypertension. In addition, we'll highlight a new program opportunity in recurrent renal stones for lumasiran, and new programs in gout, metabolic syndrome, and type 2 diabetes that are directed to highly prevalent diseases where RNAi therapeutics could have transformative potential."

Expanding Opportunities in Wild-type ATTR Amyloidosis

Alnylam will discuss the opportunity for its ATTR franchise programs with patisiran and vutrisiran in wild-type ATTR amyloidosis, a disease caused by TTR via the same pathogenic mechanism as in hereditary ATTR amyloidosis. Wild-type ATTR amyloidosis affects 200-300,000 patients worldwide representing a substantial expansion opportunity; the company will present data supporting the potential for its investigational RNAi therapeutics in this indication. Alnylam expects completion of enrollment in APOLLO-B with patisiran in early 2021 with topline data in mid-2022, while the HELIOS-B study with vutrisiran continues to enroll. Alnylam also plans to initiate in the next 12-18 months the HELIOS-C study which is aimed at evaluating vutrisiran for prevention of disease manifestations associated with ATTR amyloidosis.

Finally, Alnylam remains on track to report topline results from the HELIOS-A study of vutrisiran in early 2021. The HELIOS-A study includes a number of exploratory endpoints related to cardiac manifestations in patients with hATTR amyloidosis with polyneuropathy; the Company intends to present these data as part of the 18-month data readout in late 2021.

Harnessing the Transformative Potential of RNAi in Hypertension

RNAi therapeutics represent an opportunity to transform the treatment of hypertension with a once quarterly or bi-annually administered medicine that improves adherence and optimizes outcomes due to tonic control of blood pressure. Uncontrolled hypertension in potential target populations under evaluation comprise approximately 60 million patients in the U.S. alone.

The Company will present new clinical data from the ongoing Phase 1 study of ALN-AGT, an investigational RNAi therapeutic targeting angiotensinogen in development for the treatment of hypertension. The Phase 1 study was performed in mild-to-moderate hypertension patients who were naïve or who had washed out their anti-hypertensive medication; ALN-AGT was administered as monotherapy. In the new update, patients receiving a single dose of 400 mg or 800 mg ALN-AGT demonstrated mean serum AGT reductions of 97.5% at 4 weeks post-dose. Further, patients at the top dose demonstrated mean reductions in 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 16.8 +/- 16.3 mm Hg and 9.1 +/- 9.5 mm Hg, respectively. The safety and tolerability of ALN-AGT was consistent with data previously presented at the American Heart Association (AHA) Scientific Sessions in November 2020, with an acceptable safety profile for continued development.

Addressing NASH with the Power of Human Genetics

NASH – a leading cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma – remains an area of enormous unmet need with approximately 15 million patients in the U.S. alone. Today, existing investigational drugs in development for NASH are directed toward molecular targets lacking genetic validation. Alnylam will present an update on its lead NASH program ALN-HSD, an investigational RNAi therapeutic targeting HSD17B13 – a genetically validated target – for the treatment of NASH. The Company will review the ongoing Phase 1 study and expected timelines for human proof-of-concept in 2022. In addition, Alnylam will announce a new NASH program targeting PNPLA3, another genetically validated target. Alnylam is partnered with Regeneron in a 50-50 collaboration for the advancement of RNAi therapeutics for NASH.

Advancing the Next Wave of RNAi Therapeutics for Prevalent Diseases

During its R&D Day event, Alnylam management will introduce multiple newly disclosed, additional programs that the Company believes may comprise the "Next Wave" of investigational RNAi therapeutics for prevalent diseases. These programs include:

- Lumasiran, targeting glycolate oxidase (GO) in development for the prevention of recurrent renal stones caused by oxalate nephrolithiasis. Lumasiran is approved in the EU and U.S. for the treatment of primary hyperoxaluria Type 1, and is marketed as OXLUMO™;
- ALN-XDH, targeting xanthine dehydrogenase (XDH) in development for the treatment of gout; and
- ALN-KHK, targeting ketohexokinase (KHK) in development for the treatment of metabolic syndrome and type 2 diabetes

Delivering on the Potential for RNAi Therapeutics Beyond the Liver

Finally, Alnylam will present an update on its programs involving extra-hepatic delivery of investigational RNAi therapeutics, including opportunities for CNS, ocular and pulmonary diseases. These programs include:

- ALN-APP, targeting amyloid precursor protein (APP) in development for the treatment of autosomal dominant Alzheimer's Disease (ADAD) and cerebral amyloid angiopathy (CAA);

- ALN-HTT, targeting huntingtin protein, including exon 1, in development for the treatment of Huntington's Disease (HD); and
- ALN-COV, targeting the SARS-CoV-2 RNA genome in development for the prevention or treatment of COVID-19.

Alnylam is advancing its CNS and ocular disease programs in a 50-50 collaboration with Regeneron. Alnylam is partnered with Vir on ALN-COV.

R&D Day Webcast Information

The Company's R&D Day event will be held on Tuesday and Wednesday, December 15 and 16, 2020 from 9:00 am to 12:00 pm ET each day and will include a live video stream on the Investors section of the Company's website, www.alnylam.com. Replays will be available on the Alnylam website within 48 hours after each event. Presentations showcased during the event will be featured on Capella (www.alnylam.com/capella).

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 or disease pathway 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), and OXLUMO™ (lumasiran). Alnylam has a deep pipeline of investigational medicines, including six product candidates that are in late-stage development. Alnylam has been executing 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 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, 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 its product and pipeline goals for 2021 and the potential for RNAi therapeutics, including ONPATTRO, GIVLAARI, OXLUMO, Leqvio, patisiran, vutrisiran, fitusiran, ALN-AGT, ALN-HSD, ALN-XDH, ALN-KHK, ALN-APP, ALN-HTT and ALN-COV, its plans for additional global regulatory filings and the continuing product launches of ONPATTRO, GIVLAARI and OXLUMO, the achievement of additional pipeline milestones, including relating to the timing of topline data and potential regulatory filings for vutrisiran and the initiation of a Phase 2 study of ALN-AGT, the implications of the Phase 1 data for ALN-AGT and its potential to transform the treatment of hypertension, its expectations regarding the commercialization of Leqvio by Novartis and the continued clinical advancement of fitusiran by Sanofi, Alnylam's views with respect to the opportunity for patisiran and vutrisiran in wild-type ATTR amyloidosis, its expectations regarding the ongoing Phase 1 study of ALN-HSD and the timing for human proof-of-concept, the potential for RNAi therapeutics in prevalent diseases and to treat CNS and ocular diseases, and its belief that it has exceeded 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: 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, 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; 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; 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, and maintaining regulatory approval and obtaining pricing and reimbursement for its products, including ONPATTRO, GIVLAARI, and OXLUMO; 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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Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom
(Investors and Media)
617-682-4340

Joshua Brodsky
(Investors)
617-551-8276

Source: Alnylam Pharmaceuticals, Inc.