Alnylam Announces 2020 Product and Pipeline Goals and Provides Updates at R&D Day

November 22, 2019

− Expects to Exceed Alnylam 2020 Goals with Four Marketed Products, 14 Organic Clinical Stage Programs, Including 6 in Late-Stage Development, Across 4 Strategic Therapeutic Areas (STArs), by End of 2020 –

– Initiates HELIOS-B Phase 3 Study of Investigational Vutrisiran in ATTR Amyloidosis Cardiomyopathy –

– Announces Initial Positive Clinical Results with ALN-AAT02 and ALN-HBV02 (VIR-2218), Providing Human Proof of Concept for "Enhanced Stabilization Chemistry Plus" (ESC+) GalNAc Conjugate Delivery Technology –

– Presents Initial Positive Clinical Data for ALN-AGT, an Investigational RNAi Therapeutic for Hypertension, Expanding Opportunities for RNAi Therapeutics in Highly Prevalent Chronic Diseases –

– Reports Strong Progress in CNS and Ocular Delivery of RNAi Therapeutics with Seven Initial Programs Selected as Part of Regeneron Collaboration, Including ALN-HTT, an Investigational RNAi therapeutic for Huntington's Disease –

– Alnylam to Webcast its R&D Day Today at 8:00 a.m. ET –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 22, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, is hosting an R&D Day in New York City today. During the event, the Company plans to discuss its commercial and R&D progress, including its product and pipeline goals for 2020, focusing on the potential for global approval and/or commercialization of four RNAi therapeutic products and the advancement of six late-stage investigational programs.

Alnylam also announces today that it has initiated HELIOS-B, a global Phase 3 placebo-controlled mortality and cardiovascular hospitalization trial with investigational vutrisiran in patients with ATTR amyloidosis with cardiomyopathy. In addition, the Company is reporting initial positive clinical data with ALN-AAT02, ALN-HBV02 (VIR-2218), and ALN-AGT, representing the first human proof of concept for Alnylam's ESC+ GalNAc conjugate delivery technology – having the potential to enable greater target selectivity and a wider therapeutic index – and expansion of the Alnylam pipeline in highly prevalent chronic disease opportunities. The Company is also reporting progress in its efforts with CNS and ocular delivery of RNAi therapeutics, including an update on the status of its collaborative work with Regeneron, and announces a new investigational CNS program, ALN-HTT, in development for the treatment of Huntington's disease. Finally, Alnylam is presenting its general framework for progressing toward a self-sustainable financial profile for future growth and value creation.

"At Alnylam, we believe that we're at an exciting stage of growth, with a large number of commercial and development-stage opportunities with potentially transformative impact for patients across both rare and common diseases. Over the course of 2020 we expect to deliver on a Company profile with four medicines on the market, assuming additional regulatory approvals, while also advancing a large number of late- and earlier-stage programs, all while focusing on our pathway toward a self-sustainable financial profile. Our plans include continued global commercialization of ONPATTRO as a market-leading program, with ongoing clinical studies aimed at broadening our ATTR amyloidosis franchise to potentially address the full spectrum of disease, including the now initiated HELIOS-B study with investigational vutrisiran that we're announcing today ," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. **"**With the FDA approval just this week for GIVLAARI and through our efforts and those of our partners, we now believe that we're poised to exceed our Alnylam 2020 goals of building a multi-product, global, commercial-stage biopharma company with a deep and sustainable clinical pipeline for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact."

2020 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.
- Receive approval of ONPATTRO in Brazil in mid-2020, with planned launches in additional countries throughout 2020.
- Complete enrollment in the APOLLO-B study in late 2020.

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

- Achieve regulatory approval from the European Medicines Agency (EMA) in early 2020.
- Execute on U.S. and EU commercial launches throughout 2020.
- Report additional results from the ENVISION Phase 3 study in mid-2020.
- File for regulatory approvals and launch in additional countries in 2020.

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

- Complete enrollment in the HELIOS-A Phase 3 study in early 2020.
- Continue enrollment in the HELIOS-B Phase 3 study throughout 2020.

Lumasiran, an investigational RNAi therapeutic in development for the treatment of primary hyperoxaluria type 1 (PH1). Alnylam plans to:

- File a New Drug Application (NDA) and a Marketing Authorisation Application (MAA) with the FDA and EMA, respectively, in early 2020, assuming positive results from the ILLUMINATE-A Phase 3 study.
- Report topline results from the ILLUMINATE-B pediatric Phase 3 study in mid-2020.
- Achieve FDA and EMA regulatory approvals in late 2020.

Alnylam also plans to support The Medicines Company's continued efforts with respect to the ORION Phase 3 studies of **inclisiran**, an investigational RNAi therapeutic targeting PCSK9 in development for the treatment of hypercholesterolemia. Specifically, The Medicines Company has guided that it plans to:

- File for regulatory approval with the FDA in late 2019.
- File for regulatory approval with the EMA in early 2020.
- Continue enrollment in the ORION-4 Phase 3 CVOT study in 2020.

Alnylam also plans to support Sanofi's continued efforts in advancing **fitusiran**, an investigational RNAi therapeutic in development for the treatment of hemophilia.

In addition, the Company plans to continue advancement of its mid/earlier-stage clinical pipeline, independently or with partners, including:

- **Cemdisiran**, in development for the treatment of complement-mediated diseases, which is currently in a Phase 2 study in patients with IgA nephropathy, in addition to planned collaborative studies with Regeneron on combinations of cemdisiran with pozelimab, an anti-C5 monoclonal antibody;
- **ALN-AAT02**, in development for the treatment of alpha-1 antitrypsin deficiency-associated liver disease, which is currently in a Phase 1/2 study in healthy volunteers and patients with alpha-1 liver disease;
- **ALN-HBV02** (also known as VIR-2218), partnered with Vir and in development for the treatment of chronic hepatitis B virus (HBV) infection, which is currently in a Phase 1/2 study; and
- **ALN-AGT**, in development for the treatment of hypertension, which is currently in a Phase 1 study.
- The Company also expects to submit 3 new Investigational New Drug (IND) or equivalent applications in 2020, including for **ALN-HSD** – an investigational RNAi therapeutic targeting HSD17B13 for non-alcoholic steatohepatitis (NASH) in collaboration with Regeneron – and **ALN-LEC** – an investigational RNAi therapeutic targeting LECT2 for ALECT2 renal amyloidosis – amongst other potential programs.

HELIOS-B Phase 3 Study of Vutrisiran

Alnylam is announcing today that it has initiated the HELIOS-B Phase 3 study of vutrisiran in patients with hereditary and wild-type ATTR amyloidosis patients with cardiomyopathy. HELIOS-B will evaluate the efficacy of vutrisiran versus placebo toward the composite outcome of all-cause mortality and recurrent cardiovascular hospitalizations at 30 months, the primary study endpoint. The study protocol includes an optional interim analysis to be conducted at the Company's discretion. HELIOS-B complements the ongoing HELIOS-A Phase 3 study in patients with hereditary ATTR amyloidosis with polyneuropathy, creating a comprehensive clinical development program to evaluate the safety and efficacy of vutrisiran across the entire disease spectrum of ATTR amyloidosis.

Initial Positive Clinical Results with ESC+ GalNAc Conjugate and Highly Prevalent Chronic Disease Programs

- **ALN-AAT02 Phase 1 Results**

- Initial results demonstrate an improved hepatic safety profile for ALN-AAT02 – an ESC+ GalNAc conjugate – compared with ALN-AAT01, with robust knockdown of alpha-1 antitrypsin and favorable tolerability with no subjects showing clinically significant elevations in liver alanine transaminase levels.

- **ALN-HBV02 Phase 1/2 Results**

- Initial results demonstrate improved hepatic safety profile for ALN-HBV02 – an ESC+ GalNAc conjugate – compared with ALN-HBV01, with substantial multi-log decreases in HBsAg and favorable tolerability with no subjects or patients showing clinically significant elevations in liver alanine transaminase levels.

- **ALN-AGT Phase 1 Results**

- In the initial single-ascending dose cohorts of a Phase 1 study, ALN-AGT achieved dose-dependent lowering of angiotensinogen – a genetically defined mediator of hypertension – with robust and durable knockdown of angiotensinogen and favorable tolerability.

Progress in CNS and Ocular RNAi Therapeutic Programs and Status of Regeneron Collaboration

Alnylam is announcing today the selection of the initial seven programs in the Regeneron collaboration, including ALN-APP – an investigational RNAi therapeutic targeting amyloid precursor protein (APP) for hereditary cerebral amyloid angiopathy (hCAA) and early onset familial Alzheimer's disease (EOFAD) – and ALN-HTT – an investigational RNAi therapeutic for the treatment of Huntington's disease. In addition, the Regeneron collaboration includes an undisclosed additional CNS target program, two undisclosed ocular disease target programs, and two undisclosed liver target programs. The Regeneron collaboration is expected to achieve 1-2 new INDs per year starting in 2021, adding to the Company's expected proprietary flow of 1-2 new INDs per year.

The Company's R&D Day will be held today, November 22, 2019 from 8:00 am to 12:30 pm ET at the Westin New York at Times Square in New York City and will include a live video stream on the Investors section of the Company's website, www.alnylam.com. A replay will be available on the

Alnylam website within 48 hours after the 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 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

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), approved in the U.S., EU, Canada, Japan, and Switzerland, and GIVLAARI™ (givosiran), approved in the U.S. Alnylam has a deep pipeline of investigational medicines, including five product candidates that are in late-stage development. Alnylam is 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 employs over 1,200 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 and plans with respect to the potential for RNAi therapeutics, including lumasiran, vutrisiran, inclisiran, fitusiran, cemdisiran, ALN-AAT02, ALN-HBV02, ALN-AGT, ALN-HSD, ALN-LEC, ALN-APP, its program for Huntington’s disease and other pre-clinical programs, including in the eye and CNS, its plans for additional regulatory filings and the continuing product launch of ONPATTRO, its plans for additional regulatory filings and launch of GIVLAARI, its 2020 product and pipeline goals, including the expected timing of data readouts, regulatory filings and potential regulatory approvals, its expectations and plans with respect to a general framework for progressing toward a self-sustainable financial profile, expectations with respect to future INDs, and expectations regarding the potential to exceed 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, including ONPATTRO and GIVLAARI, progress in continuing to establish a commercial and ex-United States infrastructure, successfully launching, marketing and selling its approved products globally, including ONPATTRO and GIVLAARI, 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 and achieve a self-sustainable financial profile in the future, 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, including Regeneron, for development, manufacture and distribution of products, and Ironwood, for assistance with the education about and promotion of GIVLAARI, 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.

View source version on businesswire.com: https://www.businesswire.com/news/home/20191122005105/en/

Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom
(Investors and Media)
617-682-4340

Joshua Brodsky
(Investors)
617-551-8276