Alnylam Announces Progress with RNAi Therapeutics Platform, Including Oral Route of Administration and CNS and Ocular Delivery

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−Preclinical Proof of Concept for Oral Delivery Achieved, Demonstrating Robust, Dose-Dependent Silencing of Liver-Expressed Target in Rodents, with Durability Profile Similar to Subcutaneous Administration –

− Company Also Reports on New Advances in CNS and Ocular Delivery, Demonstrating Durable and Efficacious Target Silencing in Rodents and Non-Human Primates, with Favorable Profile Compared with Antisense Oligonucleotides (ASOs) –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 21, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today new advances in its RNAi therapeutics platform, including preclinical results demonstrating oral delivery of GalNAc-conjugated small interfering RNAs (siRNAs) – the molecules that mediate RNAi – directed to a liver target. Oral delivery could broaden the clinical and commercial opportunities for RNAi therapeutics, which are currently administered with intravenous or subcutaneous dose administration. The results were presented at the 3rdInternational Conference on the Long and the Short of Non-Coding RNAs being held June 18-23 in Crete, Greece. The Company also reported on further progress on central nervous system (CNS) and ocular delivery of novel siRNA conjugates.

“These new preclinical data are the first demonstration of functional delivery of GalNAc-siRNA conjugates via the oral route of administration, representing an important step forward in potentially advancing and expanding the clinical and commercial potential of RNAi therapeutics. Since oral delivery of GalNAc-conjugate siRNAs was achieved with use of a proprietary formulation containing a permeation enhancer, we believe that this approach can be applied to existing and future pipeline liver-directed programs, potentially creating a relatively near-term opportunity for Alnylam,” said Kevin Fitzgerald, Ph.D., Senior Vice President and Chief Scientific Officer of Alnylam. “We are equally excited to continue advancing our efforts focused on CNS and ocular delivery achieving highly durable responses, while also demonstrating favorable silencing activity of our CNS-targeted conjugate siRNA as compared to an ASO.Our CNS and ocular RNAi therapeutic programs are being advanced through our recently announced collaboration with Regeneron.”

Preclinical studies were performed to investigate the potential for oral administration of investigational RNAi therapeutics. Robust and durable messenger RNA (mRNA) silencing was observed in mice for a GalNAc-conjugated siRNA targeting Factor 12 (F12) with a proprietary formulation containing a permeation enhancer and delivered via oral gavage. The knockdown effect was sustained for over 40 days with a durability profile on par with that achieved via subcutaneous administration. Knockdown was dose-dependent and required the presence of the GalNAc conjugate and the formulation containing a permeation enhancer. Approximately 90 percent knockdown was observed upon administration of three oral doses at 3 mg/kg.

Additional data on CNS delivery of RNAi therapeutics were also presented. In rat studies, a head to head comparison of silencing activity of an siRNA and a previously reported antisense oligonucleotide (ASO) targeting human superoxide dismutase 1 (hSOD1) was performed in a transgenic model expressing hSOD1. A single intrathecal injection of a hSOD1-targeted siRNA resulted in greater silencing activity as compared to its ASO counterpart across all key anatomical regions of the brain and spinal cord. Specifically, when dosed at 0.9 mg and measured at Day 7, the hSOD1-targeted siRNA achieved superior silencing across all regions of the spine and brain, with mean silencing from 85-88 percent and 64-75 percent, respectively. In contrast, the corresponding ASO targeting hSOD1 achieved a markedly reduced level of silencing of 68-72 percent in the spine and 25-43 percent in the brain. In additional studies at a lower dose of 0.45 mg and with measurements at Day 28, the siRNA targeting hSOD1 achieved mean silencing between 67-87 percent in the spine while markedly reduced levels of silencing of 28-44 percent were observed for the ASO targeting hSOD1.

Finally, results on ocular delivery of RNAi therapeutics were also presented. Intravitreal administration of a conjugated siRNA targeting mouse transthyretin (TTR) demonstrated a dose-dependent and sustained knockdown of TTR, with maximal (greater than 95 percent) suppression achieved at doses as low as 15 micrograms per eye and lasting up to Day 135 post a single injection. Similarly, a single low intravitreal dose of a siRNA conjugate targeting human TTR resulted in virtually complete knockdown of TTR protein in the NHP eye, with effects lasting for at least three months.

To view the results presented by Alnylam at the 3rdInternational Conference on the Long and the Short of Non-Coding RNAs, please visit 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 Pharmaceuticals

Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a 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/ocular diseases. Based on Nobel Prizewinning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. ONPATTRO® (patisiran) is the first-ever RNAi therapeutic approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults and by the EMA for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2

polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including five product candidates in Phase 3 studies and one in registration. 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. Headquartered in Cambridge, MA, Alnylam employs over 1,200 people worldwide. 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 broadened clinical and commercial opportunity for oral delivery of RNAi therapeutics directed to liver targets, relative to the opportunity for intravenous and subcutaneous delivery of such therapeutics, the anticipated durability of such RNAi therapeutics administered by oral delivery, and the continued advancement of Alnylam's efforts focused on CNS and ocular delivery of investigational RNAi therapeutics in preclinical models, and expectations regarding "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.

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