Alnylam Reports Additional Positive Interim Phase 1 Results for ALN-APP, in Development for Alzheimer's Disease and Cerebral Amyloid Angiopathy

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– Single Doses of ALN-APP Achieve Sustained Pharmacodynamic Activity up to 10 Months After Administration –

– Observed Marked Reductions in $A\beta_{42}$ and $A\beta_{40}$, Amyloid Fragments Implicated in Alzheimer's Disease and Cerebral Amyloid Angiopathy –

– First Patient Dosed in Multiple-dose Part B Portion of Study, with the Study Proceeding in Canada, UK, and the Netherlands –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 25, 2023-- Alnylam Pharmaceuticals, Inc. (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=53675237&newsitemid=20231025380274&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=6f8b4541c3272bea5ba26baa78d6232f) (Nasdaq: ALNY) today announced additional positive interim results for the ongoing single ascending dose portion of the Phase 1 study of ALN-APP, an investigational RNAi therapeutic targeting amyloid precursor protein (APP) in development for the treatment of Alzheimer's disease and cerebral amyloid angiopathy (CAA). The data were presented today in a late-breaker session at the 16th Clinical Trials on Alzheimer's Disease (CTAD) conference, being held October 24-27, 2023, in Boston, MA. ALN-APP is the first clinical-stage program using Alnylam's proprietary C16-siRNA conjugate platform for central nervous system (CNS) delivery and the first investigational RNAi therapeutic to demonstrate gene silencing in the human brain. ALN-APP is being developed in collaboration with Regeneron.

"Today's results showcase the exciting emerging profile of ALN-APP. This novel approach appears generally well-tolerated and is able to target the amyloid pathway successfully, robustly lowering target engagement biomarkers sAPPα and sAPPβ and maintaining a significant effect up to 10 months after administration," said Dr. Cath Mummery, Consultant Neurologist and Head of Clinical Trials, Dementia Research Centre, University College London. "For the first time, we also see that single doses of ALN-APP can reduce cerebral spinal fluid levels of $A\beta_{42}$ and $A\beta_{40}$, which are the amyloidogenic peptides that are the primary components of amyloid deposits in Alzheimer's disease and CAA. This approach warrants further study to evaluate whether it can potentially interrupt relentless progression of these two devastating diseases."

Twenty patients have been enrolled in three single-dose cohorts in Part A of the ongoing Phase 1 study in patients with early-onset Alzheimer's disease. In this study to date, blinded single doses of ALN-APP, which are administered by intrathecal injection, have been well tolerated. All adverse events were mild or moderate in severity. Cerebral spinal fluid (CSF) safety biomarkers, routine labs, and the exploratory biomarker neurofilament light chain (NfL) all continue to show no concerning trends. Patients treated with a single dose of 75mg ALN-APP experienced rapid and sustained reduction in CSF of both soluble APPα (sAPPα) and soluble APPβ (sAPPβ), biomarkers of target engagement, with maximum reductions of 84% and 90%, respectively. These effects were highly durable, with mean reductions in sAPPα and sAPPβ of 33% and 39%, respectively, at 10 months after a single 75mg dose. Available data on exploratory disease-related biomarkers showed robust reductions in CSF of $A\beta_{42}$ and $A\beta_{40}$, the soluble forms of the amyloidogenic peptides that aggregate into amyloid deposits in AD and CAA. At two months after a single dose of 75mg ALN-APP, mean reductions in CSF $A\beta_{42}$ and $A\beta_{40}$ were 49% and 71%, respectively.

Further exploration of single doses of ALN-APP is ongoing in Part A. In addition, the first patient has now been dosed in Part B, the multiple-dose part of the study. Part B was previously initiated in Canada and has also now received all required approvals to proceed in the UK and the Netherlands. The multiple dose part of the study remains on partial clinical hold in the U.S. due to findings observed in non-clinical chronic toxicology studies.

"These additional interim data further illustrate the potential for RNAi therapeutics to set a new standard for silencing disease-causing genes in the CNS, providing evidence that a single dose of ALN-APP can achieve deep target engagement, a long duration of action, and an encouraging early safety profile," said Tim Mooney, Director, ALN-APP Program Leader at Alnylam. "The robust lowering we see in $A\beta_{42}$ and $A\beta_{40}$ shows that reducing APP protein production with RNAi can reduce these downstream disease-associated peptides and gives us confidence as we proceed with Part B of the Phase 1 study and further explore the opportunity for ALN-APP in both Alzheimer's disease and CAA."

Successful human translation of the C16-siRNA conjugate platform is unlocking a broader portfolio of CNS programs. In addition to ALN-APP, Alnylam and Regeneron have named 10 targets in the CNS as part of their exclusive collaboration established in 2019 to discover RNAi therapeutics for CNS and ocular diseases.

About the Phase 1 Study of ALN-APP

The Phase 1 study is a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamic effects of ALN-APP in patients with early-onset Alzheimer's disease (EOAD). The study is being conducted in two parts: single ascending dose phase (Part A) and multiple dose phase (Part B) in patients with EOAD. The planned enrollment for this study is up to 60 patients.

The interim readout of the Phase 1 study of ALN-APP is focused on assessing safety, tolerability and levels of target engagement biomarkers, sAPPα and sAPPβ.

About ALN-APP

ALN-APP is an investigational, intrathecally administered RNAi therapeutic targeting amyloid precursor protein (APP) in development for the treatment of Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). Genetic mutations that increase production of APP or alter its cleavage cause early-onset AD, early-onset CAA, or both. ALN-APP is designed to decrease APP mRNA in the central nervous system (CNS), to decrease synthesis of APP protein and all downstream intracellular and extracellular APP-derived cleavage products, including amyloid beta (Aβ). Reducing APP protein production is expected to reduce the secretion of Aβ peptides that aggregate into extracellular amyloid deposits and reduce the intraneuronal APP cleavage products that trigger the formation of neurofibrillary tangles and cause neuronal dysfunction in Alzheimer's disease. ALN-APP is the first program utilizing Alnylam's proprietary C16-siRNA

conjugate technology, which enables enhanced delivery to cells in the CNS. This program is being developed in collaboration with Regeneron Pharmaceuticals. The safety and efficacy of ALN-APP have not been evaluated by the FDA, EMA, or any other health authority.

About Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common form of dementia, affecting over 30 million people worldwide. AD is characterized by progressive memory loss and cognitive decline, with neuropathological accumulation of amyloid plaques, neurofibrillary tangles, and neuroinflammation, ultimately resulting in significant brain atrophy. Disease progression results in progressive loss of independence, increased caregiver burden, institutionalization, and premature death. Early-onset Alzheimer's disease (EOAD) refers to a subgroup of AD with symptom onset prior to the age of 65, representing approximately 4% to 6% of all AD. EOAD is the leading cause of dementia in younger individuals and is a significant cause of disability and early mortality. Available treatment options include symptomatic treatment and treatment to reduce amyloid deposits in the brain. There are currently no available treatments that have been shown to halt or reverse the progression of the disease.

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 Pharmaceuticals (Nasdaq: ALNY) has led 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 and prevalent diseases with unmet need. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach yielding transformative medicines. Since its founding in 2002, Alnylam has led the RNAi Revolution and continues to deliver on a bold vision to turn scientific possibility into reality. Alnylam's commercial RNAi therapeutic products are ONPATTRO® (patisiran), AMVUTTRA® (vutrisiran), GIVLAARI® (givosiran), OXLUMO® (lumasiran), and Leqvio® (inclisiran), which is being developed and commercialized by Alnylam's partner, Novartis. Alnylam has a deep pipeline of investigational medicines, including multiple 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 (https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=53675237&newsitemid=20231025380274&lan=en-US&anchor=www.alnylam.com&index=2&md5=70283f3ab2758f2bbb034de1c75a38e6) and engage with us on X (formerly Twitter) at @Alnylam (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Ftwitter.com%2FAlnylam&esheet=53675237&newsitemid=20231025380274&lan=en-US&anchor=%40Alnylam&index=3&md5=027e1c7f36e165d48cce2b4e5e6ced06), on LinkedIn (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.linkedin.com%2Fcompany%2Falnylam-pharmaceuticals%2F&esheet=53675237&newsitemid=20231025380274&lan=en-US&anchor=LinkedIn&index=4&md5=c12989426f0183079d304d4823a89c23), or on Instagram (https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.instagram.com%2Falnylampharma%2F&esheet=53675237&newsitemid=20231025380274&lan=en-US&anchor=Instagram&index=5&md5=5d5bfbcf3ed12fd590cc5753626c3405).

Alnylam Forward Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, expectations regarding Alnylam's aspiration to become a leading biotech company and the planned achievement of its "*Alnylam P^{5}x25*" strategy, the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, including ALN-APP, Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam's projected commercial and financial performance, should be considered forward-looking statements. 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; Alnylam's ability to successfully execute on its "*Alnylam P^{5}x25*" strategy; 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 Alnylam's product candidates, including vutrisiran; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, including vutrisiran, as well as favorable pricing and

reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; delays or interruptions in the supply of resources needed to advance Alnylam's research and development programs, including as may arise from recent disruptions in the supply of non-human primates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the indication AMVUTTRA 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 Roche, Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the risks of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's 2022 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as may be updated from time to time in Alnylam's subsequent Quarterly Reports on Form 10-Q 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 press release discusses investigational RNAi therapeutics and is not intended to convey conclusions about efficacy or safety as to those investigational therapeutics. There is no guarantee that any investigational therapeutics will successfully complete clinical development or gain health authority approval.

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