



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

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- First Clinical Study of a Central Nervous System-Administered RNAi Therapeutic Showed Rapid and Robust Target Engagement with Sustained Effect Over 6 Months with a Single Dose –*
- ALN-APP Continues to Demonstrate an Encouraging Clinical Safety and Tolerability Profile –*
- Multiple-dose Portion of Study, Part B, Being Initiated in Approved Regions –*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 17, 2023-- Alnylam Pharmaceuticals, Inc. (<https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=53457146&newsitemid=20230716241827&lan=en-US&anchor=Alnylam+Pharmaceuticals%2C+Inc.&index=1&md5=39c8a1c999f849fa2cad6c942c24cb7c>) (Nasdaq: ALNY) announced today updated 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 results were presented at the 2023 Alzheimer's Association International Conference (AAIC) being held July 16-20, 2023 in Amsterdam, The Netherlands. 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 Pharmaceuticals, Inc.

Twenty patients with early-onset Alzheimer's disease have been enrolled in three single-dose cohorts in Part A of the ongoing Phase 1 study. In this study to date, single doses of ALN-APP, which are administered by intrathecal injection, have been well tolerated. All adverse events were mild or moderate in severity. Cerebrospinal fluid (CSF) white blood cell count and total protein levels showed no remarkable elevations from baseline. Routine laboratory assessments (hematology, serum chemistry, liver function, urinalysis, coagulation) as well as preliminary data for the exploratory biomarker neurofilament light chain (NfL) did not reveal any significant abnormalities. Patients treated with a single dose of 75mg ALN-APP experienced a rapid and sustained reduction in cerebrospinal fluid of both soluble APP α (sAPP α) and soluble APP β (sAPP β), biomarkers of target engagement, with maximum reductions of 84% and 90%, respectively. Mean reductions in sAPP α of greater than 55% and sAPP β greater than 65% were sustained at 6 months after a single dose. Additional results can be seen in the presentation on Capella (<https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fcapella.alnylam.com%2F2023%2F07%2F17%2Fapp-aaic-2023&esheet=53457146&newsitemid=20230716241827&lan=en-US&anchor=Capella&index=2&md5=22c3cb1c2c67bc359987da84354c7383>).

"We've known for decades that mutations that increase APP production, or alter its proteolysis, cause early-onset Alzheimer's disease, early-onset CAA or both," said Dr. Sharon Cohen, MD, FRCP, Neurologist and Medical Director, Toronto Memory Program. "These Phase 1 results show that a single dose of ALN-APP can rapidly reduce APP production and that this effect is sustained at 6 months. Given the critical need for new and better treatments for AD and CAA, these results are promising, and the approach warrants further study."

Further exploration of single doses of ALN-APP is ongoing in Part A. In addition, the safety review committee has recommended initiation of Part B, the multiple-dose part of the study. Part B will enroll patients from Part A and has already received regulatory approval to proceed in Canada, where the majority of the Part A clinical trial patients were enrolled. The multiple dose part of the study remains on partial clinical hold in the U.S. due to findings observed in prior non-clinical chronic toxicology studies.

“The rapid, robust, and sustained target engagement that we have achieved with a single dose of ALN-APP and the encouraging interim safety data to date illustrate the potential of RNAi therapeutics to set a new standard for silencing disease-causing genes in the CNS and target diseases like AD and CAA upstream of existing therapies,” said Tim Mooney, Director, ALN-APP Program Leader at Alnylam. “We are excited to initiate the multiple dose part of the Phase 1 study and learn more about the potential of this new approach for these devastating diseases.”

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 eye and CNS 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, sAPP α and sAPP β .

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 (A β). Reducing APP protein production is expected to reduce the secretion of A β 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 ONPATPRO® (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 P⁵x25*" 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=53457146&newsitemid=20230716241827&lan=en-](https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com&esheet=53457146&newsitemid=20230716241827&lan=en-US&anchor=www.alnylam.com&index=3&md5=8e200db661cf33abe56d3c2eb71dfc68)

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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 P⁵x25*" 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: Alnylam's ability to successfully execute on its "*Alnylam P⁵x25*" 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, including ALN-APP; the pre-clinical and clinical results for Alnylam's product candidates, including patisiran and vutrisiran; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, including patisiran and vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; 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; 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 for ONPATTRO or 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 Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of a current government investigation and the risk 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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